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(54) Title: RB PAHTWAY AND CHROMATIN REMODELING GENES THAT ANTAGONIZE *LET-60* RAS SIGNALING

(57) Abstract: In general, the invention provides methods and compositions useful in the treatment of a neoplasia. These compositions include new components of the Rb pathway that function in chromatin remodeling and antagonize Ras signaling.

WO 2004/024084 A2

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characterized. Loss-of-function mutations in two functionally redundant pathways that are encoded by the class A and class B synthetic multivulva (synMuv) genes also cause a Muv phenotype.

In addition to LIN-35 Rb, other proteins with class B synMuv activity
5 are homologous to mammalian Rb-associated proteins. These other proteins include DPL-1 and EFL-1, homologs of DP and E2F transcription factors, LIN-53, a homolog of the Rb-binding proteins RbAp46 and RbAp48, HDA-1, a histone deacetylase homolog and HPL-2, a heterochromatin protein 1 homolog. The class B synMuv proteins act together to negatively regulate the
10 transcription of genes that promote vulval development. Initially, DPL-1 and EFL-1 heterodimers bind DNA at specific regulatory sequences of vulval cell-fate determination genes. DNA-bound DPL-1 and EFL-1 heterodimers recruit LIN-35 Rb, which in turn recruits proteins that act to remodel chromatin. One of these proteins, HDA-1, is predicted to deacetylate lysines of nucleosomal
15 histones. Deacetylation of lysine residues is required for their subsequent methylation. HPL-2, another protein that may be recruited by LIN-35 Rb, is expected to act like other HP1 family proteins and bind, via its chromodomain, to methylated lysine residues of nucleosomal histones.

Given the similarities that exist between *C. elegans* and mammalian Rb
20 and Ras pathways, *C. elegans* provides an efficient, inexpensive, and facile screening tool to identify novel clinical targets and chemotherapeutics useful in the treatment of neoplasia.

Summary of the Invention

25 The invention provides compositions useful in treating a neoplasia and methods for identifying chemotherapeutic agents.

In one aspect, the invention features a method for identifying a compound that treats a neoplasia, the method involves (a) contacting a cell containing a mutation in a Class B synMuv gene selected from the group
30 consisting of: *mep-1*, *lin(n3628)*, *lin(n4256)*, and *lin-65* and a second mutation

in a synthetic multivulval gene, or an ortholog thereof, with a candidate compound; and (b) detecting a phenotypic alteration in the contacted cell relative to a control cell; where a candidate compound that alters the phenotype of the contacted cell relative to the control cell is a compound that treats a neoplasia. In one embodiment, the cell is in a nematode. In another embodiment, the phenotypic alteration is an alteration in a multivulval phenotype. In another embodiment, the phenotypic alteration is an alteration in sterility. In another embodiment, the second mutation is in a synMuv class A gene. In another embodiment, the cell is an isolated mammalian cell. In another embodiment, the phenotypic alteration is a decrease in cell proliferation.

In another aspect, the invention provides a method for identifying a candidate compound that treats a neoplasia, the method involves (a) providing a cell having a mutation in a Class B synMuv gene selected from the group consisting of *mep-1*, *lin(n3628)*, *lin(n4256)*, and *lin-65* and having a second mutation in a synMuv nucleic acid or ortholog thereof; (b) contacting the cell with a candidate compound; and (c) detecting a decrease in proliferation of the cell contacted with the candidate compound relative to a control cell not contacted with the candidate compound, where a decrease in proliferation identifies the candidate compound as a candidate compound that treats a neoplasia. In one embodiment, the cell is in a nematode. In another embodiment, the decrease in proliferation is detected by detecting inhibition of a Muv phenotype. In another embodiment, the cell has a mutation in Dp, E2F, or histone deacetylase. In another embodiment, the cell is an isolated mammalian cell.

In another aspect, the invention provides a method of identifying a compound that treats a neoplasia, the method involves (a) providing a cell expressing a nucleic acid having at least 95% identity to a Class B synMuv gene selected from the group consisting of: *mep-1*, *lin(n3628)*, *lin(n4256)*, and *lin-65*; (b) contacting the cell with a candidate compound; and (c) monitoring

the expression of the nucleic acid, an alteration in the level of expression of the nucleic acid indicates that the candidate compound is a compound that treats a neoplasia. In one embodiment, the gene contains a reporter gene (e.g., *lacZ*, *gfp*, CAT, or luciferase). In another embodiment, expression is monitored by
5 assaying protein level. In another embodiment, the expression is monitored by assaying nucleic acid level. In yet another embodiment, the cell is in a nematode.

In another aspect, the invention features a method for identifying a candidate compound that treats a neoplasia, the method involves (a) providing
10 a cell expressing a Class B synMuv gene selected from the group consisting of: *mep-1*, *lin(n3628)*, *lin(n4256)*, and *lin-65*; (b) contacting the cell with a candidate compound; and (c) comparing the expression of the polypeptide in the cell contacted with the candidate compound to a control cell not contacted with the candidate compound, where an increase in the expression of the
15 polypeptide identifies the candidate compound as a candidate compound that treats a neoplasia. In one embodiment, the cell is in a nematode. In another embodiment, the expression is monitored with an immunological assay.

In another aspect, the invention features a method for identifying a candidate compound that treats a neoplasia, the method involves (a) providing
20 a cell expressing a Class B synMuv polypeptide selected from the group consisting of: MEP-1, LIN(n3628), LIN(n4256), and LIN-65, the method involves; (b) contacting the cell with a candidate compound; and (c) comparing the biological activity of the polypeptide in the cell contacted with the candidate compound to a control cell not contacted with the candidate
25 compound, where an increase in the biological activity of the polypeptide identifies the candidate compound as a candidate compound that treats a neoplasia. In another embodiment, the biological activity is monitored with an enzymatic assay. In another embodiment, the biological activity is monitored with an immunological assay. In yet another embodiment, the biological
30 activity is monitored with a nematode bioassay.

In another aspect, the invention features a method of identifying a nucleic acid target of class B synMuv biological activity, the method involves (a) mutagenizing a *C. elegans* containing mutations in a Class B synMuv gene selected from the group consisting of: *mep-1*, *lin(n3628)*, *lin(n4256)*, and *lin-65* and in a Class A synMuv gene; (b) allowing the *C. elegans* to reproduce; and (c) selecting a *C. elegans* containing a mutation that suppresses a synMuv phenotype; where the mutation identifies a nucleic acid target of class B synMuv biological activity.

In another aspect, the invention features a method of identifying a nucleic acid target of class B synMuv biological activity, the method involves (a) providing a microarray containing fragments of nematode nucleic acids; (b) contacting the microarray with detectably labeled nucleic acids derived from a nematode containing a mutation in a Class B synMuv gene selected from the group consisting of: *mep-1*, *lin(n3628)*, *lin(n4256)*, and *lin-65* gene; (c) detecting an alteration in the expression of at least one nucleic acid of a *C. elegans* containing a mutation in the Class B synMuv gene relative to the expression of the nucleic acid in a control nematode, where an alteration in the expression identifies the nucleic acid as a nucleic acid target of class B synMuv biological activity. In one embodiment, the *C. elegans* further contains a mutation in a second synMuv gene. In another embodiment, the *C. elegans* further contains a mutation in a gene that results in a Vulvaless (Vul) phenotype.

In another aspect, the invention features a method for identifying a nucleic acid that binds a synMuv class B polypeptide, the method involves (a) providing nucleic acids derived from a nematode cell; (b) crosslinking the nucleic acids and their associated proteins to form a nucleic acid-protein complex; (c) contacting the nucleic acid-protein complex with an antibody against a polypeptide selected from the group consisting of MEP-1, LIN(n3628), LIN(n4256), and LIN-65; (d) purifying the nucleic acid-protein complex using an immunological method; and (e) isolating the nucleic acid,

where the isolated nucleic acid is a nucleic acid that binds a synMuv class B polypeptide. In one embodiment, the method further involves the following steps: (f) detectably labeling the nucleic acid of step (e); (g) contacting a microarray containing *C. elegans* nucleic acid fragments with the detectably labeled nucleic acid; and (h) detecting binding of the detectably labeled nucleic acid, where the binding identifies the nucleic acid as a nucleic acid that binds a synMuv class B polypeptide.

In another aspect, the invention provides a vector containing a nucleic acid having at least 95% identity to a Class B synMuv gene selected from the group consisting of: *mep-1*, *lin(n3628)*, *lin(n4256)*, and *lin-65*. In one embodiment, the synMuv gene is *mep-1* (SEQ ID NO:2). In one embodiment, the synMuv gene contains a mutation selected from the group consisting of *n3680*, *n3702*, and *n3703*. In other embodiments, the synMuv gene is *lin(n3628)* (SEQ ID NO:24), *lin(n4256)* (SEQ ID NO:26), or *lin-65* (SEQ ID NO:28).

In another aspect, the invention provides an isolated cell containing the vector of the previous aspect.

In a related aspect, the invention provides a nematode containing the nucleic acid of the previous aspect.

In another aspect, the invention provides a nematode containing a mutation in a Class B synMuv gene selected from the group consisting of: *mep-1*, *lin(n3628)*, *lin(n4256)*, and *lin-65*. In one embodiment, the mutation is a *mep-1* mutation selected from the group consisting of *n3680*, *n3702*, and *n3703*.

In another aspect, the invention features a purified nucleic acid containing a sequence that hybridizes under high stringency conditions to a Class B synMuv nucleic acid selected from the group consisting of: *mep-1*, *lin(n3628)*, *lin(n4256)*, and *lin-65*.

In another aspect, the invention features an antibody against a Class B synMuv polypeptide selected from the group consisting of: MEP-1, LIN(n3628), LIN(n4256), and LIN-65.

5 In another aspect, the invention provides a method for identifying a compound that treats a condition characterized by inappropriate cell death, the method involves (a) contacting a nematode containing a mutation in a Class B synMuv gene selected from the group consisting of: *mep-1*, *lin(n3628)*, *lin(n4256)*, and *lin-65* with a candidate compound; and (b) detecting a muv phenotype in the contacted nematode relative to a control nematode; where a
10 candidate compound that alters the phenotype of the contacted nematode relative to the control nematode is a compound that treats a condition characterized by inappropriate cell death. In one embodiment, the cell is in a nematode. In another embodiment, the alteration is an alteration in a synMuv phenotype.

15 In another aspect, the invention provides a method for identifying a compound that treats a neoplasia, the method involves (a) contacting a cell containing a mutation in a gene encoding KIAA1732 and a second mutation in a synMuv nucleic acid, or an ortholog thereof, with a candidate compound; (b) detecting a phenotypic alteration in the contacted cell relative to a control cell;
20 where a candidate compound that alters the phenotype of the contacted cell relative to the control cell is a compound that treats a neoplasia. In one embodiment, the synthetic multivulval gene is a synMuv class A gene. In another embodiment, the cell is an isolated mammalian cell. In another embodiment, the phenotypic alteration is a decrease in cell proliferation.

25 In another aspect, the invention features a method for identifying a candidate compound that treats a neoplasia, the method involves (a) providing a cell having a mutation in a nucleic acid encoding KIAA1732 and having a second mutation in a synMuv nucleic acid, or ortholog thereof; (b) contacting the cell with a candidate compound; and (c) detecting a decrease in
30 proliferation of the cell contacted with the candidate compound relative to a

control cell not contacted with the candidate compound, where a decrease in proliferation identifies the candidate compound as a candidate compound that treats a neoplasia. In one embodiment, the cell has a mutation in Dp, E2F, or histone deacetylase. In another embodiment, the cell is an isolated mammalian cell.

In another aspect, the invention provides a method of identifying a compound that treats a neoplasia, the method involves (a) providing a cell expressing a nucleic acid having at least 95% identity to a nucleic acid that encodes KIAA1732; (b) contacting the cell with a candidate compound; and (c) monitoring the expression of the nucleic acid, an alteration in the level of expression of the nucleic acid indicates that the candidate compound is a compound that treats a neoplasia. In one embodiment, the gene contains a reporter gene (e.g., *lacZ*, *gfp*, CAT, or luciferase). In another embodiment, expression is monitored by assaying protein level. In another embodiment, the expression is monitored by assaying nucleic acid level. In another embodiment, the cell is an isolated mammalian cell.

In another aspect, the invention provides a method for identifying a candidate compound that treats a neoplasia, the method involves (a) providing a cell expressing a KIAA1732 polypeptide; (b) contacting the cell with a candidate compound; and (c) comparing the expression of the polypeptide in the cell contacted with the candidate compound to a control cell not contacted with the candidate compound, where an increase in the expression of the polypeptide identifies the candidate compound as a candidate compound that treats a neoplasia. In one embodiment, the cell is an isolated mammalian cell. In another embodiment, the expression is monitored with an immunological assay.

In another aspect, the invention features a method for identifying a candidate compound that treats a neoplasia, the method involves (a) providing a cell expressing a KIAA1732 polypeptide; (b) contacting the cell with a candidate compound; and (c) comparing the biological activity of the

polypeptide in the cell contacted with the candidate compound to a control cell not contacted with the candidate compound, where an increase in the biological activity of the polypeptide identifies the candidate compound as a candidate compound that treats a neoplasia. In one embodiment, the biological activity is monitored with an enzymatic assay. In another embodiment, the biological activity is monitored with an immunological assay. In another embodiment, the biological activity is methyl transferase activity.

In another aspect, the invention features a method for identifying a nucleic acid that binds KIAA1732, the method involves (a) providing nucleic acids derived from a mammalian cell; (b) crosslinking the nucleic acids and their associated proteins to form a nucleic acid-protein complex; (c) contacting the nucleic acid-protein complex with an anti-KIAA1732 antibody; (d) purifying the nucleic acid-protein complex using an immunological method; and (e) isolating the nucleic acid, where the isolated nucleic acid is a nucleic acid that binds KIAA1732. In one embodiment, the method further involves the following steps: (f) detectably labeling the nucleic acid of step (e); (g) contacting a microarray containing human nucleic acid fragments with the detectably labeled nucleic acid; and (h) detecting binding of the detectably labeled nucleic acid, where the binding identifies the nucleic acid as a nucleic acid that binds KIAA1732.

In another aspect, the invention provides a vector containing a nucleic acid having at least 95% identity to SEQ ID NO:36.

In another aspect, the invention provides an isolated cell containing the vector of the previous aspect.

In another aspect, the invention provides a method for identifying a compound that treats a neoplasia, the method involves (a) contacting a nematode containing a mutation in a Class C synMuv gene selected from the group consisting of *trr-1*, *hat-1*, *epc-1*, and *ssl-1* with a candidate compound; and (b) detecting an altered phenotype in the contacted nematode relative to a control nematode; where a candidate compound that alters the phenotype of

the contacted nematode relative to the control nematode is a compound that treats a neoplasia. In one embodiment, the alteration is an alteration in vulval phenotype. In another embodiment, the alteration is an alteration in sterility. In another embodiment, the synMuv class C gene is *trr-1*. In another
5 embodiment, the mutations are selected from the group consisting of *n3630*, *n3637*, *n3704*, *n3708*, *n3709*, and *n3712*.

In another aspect, the invention provides a method for identifying a candidate compound that treats a neoplasia, the method involves (a) providing a cell having a mutation in a Class C synMuv gene selected from the group
10 consisting of *trr-1*, *hat-1*, *epc-1*, and *ssl-1* and having a second mutation in a synMuv nucleic acid or ortholog thereof; (b) contacting the cell with a candidate compound; and (c) detecting a decreased proliferation of the cell contacted with the candidate compound relative to a control cell not contacted with the candidate compound, where a decrease in proliferation identifies the
15 candidate compound as a candidate compound that treats a neoplasia. In one embodiment, the cell is in a nematode. In another embodiment, the nematode displays an alteration in a synMuv phenotype. In another embodiment, the cell contains a mutation in a class A or class B synMuv gene.

In another aspect, the invention provides a method for identifying a
20 compound that treats a neoplasia, the method involves (a) contacting a nematode containing a mutation in a Class C synMuv gene selected from the group consisting of *trr-1*, *hat-1*, *epc-1*, and *ssl-1* and a second mutation in a Class A synthetic multivulval gene with a candidate compound; and (b) detecting an altered phenotype in the contacted nematode relative to a control
25 nematode; where a candidate compound that alters the phenotype of the contacted nematode relative to the control nematode is a compound that treats a neoplasia. In one embodiment, the alteration is an alteration in synMuv phenotype. In another embodiment, the alteration is an alteration in sterility.

In another aspect, the invention provides a method for identifying a
30 compound that treats a neoplasia, the method involves (a) contacting a

nematode containing a mutation in a Class C synMuv gene selected from the group consisting of *trr-1*, *hat-1*, *epc-1*, and *ssl-1* and a second mutation in a Class B synthetic multivulval gene with a candidate compound; (b) detecting an altered phenotype in the contacted nematode relative to a control nematode; where a candidate compound that alters the phenotype of the contacted nematode relative to the control nematode is a compound that treats a neoplasia. In another embodiment, the alteration is an alteration in synMuv phenotype. In another embodiment, the alteration is an alteration in sterility. In another aspect, the invention features a method for identifying a candidate compound that treats a neoplasia, the method involves (a) providing a cell having a mutation in a Class C synMuv gene selected from the group consisting of *trr-1*, *hat-1*, *epc-1*, and *ssl-1* and having a second mutation in a synMuv gene or ortholog thereof; (b) contacting the cell with a candidate compound; and (c) detecting a decreased proliferation of the cell contacted with the candidate compound relative to a control cell not contacted with the candidate compound, where a decrease in proliferation identifies the candidate compound as a candidate compound that treats a neoplasia. In one embodiment, the cell is in a nematode. In another embodiment, the nematode displays an alteration in a synMuv phenotype.

In another aspect, the invention provides a method of identifying a compound that treats a neoplasia, the method involves (a) providing a cell expressing a nucleic acid having at least 95% identity to a Class C synMuv nucleic acid selected from the group consisting of *trr-1*, *hat-1*, *epc-1*, and *ssl-1*; (b) contacting the cell with a candidate compound; and (c) monitoring the expression of the nucleic acid, an alteration in the level of expression of the nucleic acid indicates that the candidate compound is a compound that treats a neoplasia. In one embodiment, the gene contains a reporter gene. In another embodiment, the reporter gene contains *lacZ*, *gfp*, CAT, or luciferase. In another embodiment, the expression is monitored by assaying protein level. In

yet another embodiment, the expression is monitored by assaying nucleic acid level. In yet another embodiment, the nucleic acid is in a nematode.

In another aspect, the invention provides a method for identifying a candidate compound that treats a neoplasia, the method involves (a) providing
5 a cell expressing a a Class C synMuv polypeptide selected from the group consisting of TRR-1, HAT-1, EPC-1, and SSL-1 polypeptide; (b) contacting the cell with a candidate compound; and (c) comparing the expression of the polypeptide in the cell contacted with the candidate compound to a control cell not contacted with the candidate compound, where an increase in the
10 expression of the polypeptide identifies the candidate compound as a candidate compound that treats a neoplasia. In one embodiment, the cell is in a nematode. In another embodiment, the expression is monitored with an immunological assay.

In another aspect, the invention provides a method for identifying a
15 candidate compound that treats a neoplasia, the method involves (a) providing a cell expressing a Class C synMuv polypeptide selected from the group consisting of TRR-1, HAT-1, EPC-1, and SSL-1; (b) contacting the cell with a candidate compound; and (c) comparing the biological activity of the polypeptide in the cell contacted with the candidate compound to a control cell
20 not contacted with the candidate compound, where an increase in the biological activity of the polypeptide identifies the candidate compound as a candidate compound that treats a neoplasia. In one embodiment, the cell is in a nematode. In another embodiment, the biological activity is monitored with an enzymatic assay. In another embodiment, the biological activity is monitored
25 with an immunological assay.

In another aspect, the invention provides a method of identifying a nucleic acid target of a synMuv Class C polypeptide, the method involves (a) mutagenizing a *C. elegans* containing a first mutation in a Class C synMuv gene selected from the group consisting of *trr-1*, *hat-1*, *epc-1*, and *ssl-1* and a
30 second mutation in a Class A or Class B synMuv gene; (b) allowing the *C.*

elegans to reproduce; (c) selecting a *C. elegans* containing a mutation that suppresses a synMuv phenotype; where the mutation identifies a nucleic acid target of a synMuv class C polypeptide. In one embodiment, the second mutation is in a class A synMuv gene. In another embodiment, the second
5 mutation is in a Class B synMuv gene.

In another aspect, the invention provides a method for identifying a nucleic acid target of a synMuv Class C polypeptide, the method involves (a) providing a *C. elegans* containing a mutations in a Class C synMuv gene selected from the group consisting of *trr-1*, *hat-1*, *epc-1*, and *ssl-1*; (b) growing
10 the *C. elegans* on bacteria expressing a dsRNA; and (c) identifying a dsRNA that suppresses a synMuv phenotype; where the dsRNA identifies a nucleic acid target of a synMuv class C polypeptide.

In another aspect, the invention provides a method for identifying a nucleic acid target of a synMuv class C polypeptide, the method involves (a)
15 providing a *C. elegans* containing mutations in a Class C synMuv gene selected from the group consisting of *trr-1*, *hat-1*, *epc-1*, and *ssl-1* and in a Class A or Class B synMuv gene; (b) growing the *C. elegans* on bacteria expressing a dsRNA; and (c) identifying a dsRNA that suppresses a synMuv phenotype; where the dsRNA identifies a nucleic acid target of a synMuv class C
20 polypeptide.

In another aspect, the invention features a method of identifying a nucleic acid whose expression is modulated by a synMuv class C polypeptide, the method involves (a) providing a microarray containing fragments of nematode nucleic acids; (b) contacting the microarray with detectably labeled
25 nucleic acids derived from a nematode containing a mutation in a Class C synMuv gene selected from the group consisting of *trr-1*, *hat-1*, *epc-1*, and *ssl-1* gene; (c) detecting an alteration in the expression of at least one nucleic acid of a *C. elegans* containing a mutation in the synMuv class C gene relative to the expression of the nucleic acid in a control nematode, where an alteration in
30 the expression identifies the nucleic acid as a nucleic acid modulated by a

synMuv class C polypeptide. In one embodiment, the *C. elegans* further contains a mutation in a synMuv A or synMuv B gene. In another embodiment, the *C. elegans* further contains a mutation in a gene that results in a Vulvaless (Vul) phenotype. In another embodiment, the gene encodes LET-60.

In another aspect, the invention provides a method for identifying a nucleic acid target of a synMuv class C polypeptide, the method involves (a) providing nucleic acids derived from a nematode cell; (b) crosslinking the nucleic acids and their associated proteins to form a nucleic acid-protein complex; (c) contacting the nucleic acid-protein complex with an antibody that binds a polypeptide selected from the group consisting of TRR-1, HAT-1, EPC-1, AND SSL-1; (d) purifying the nucleic acid-protein complex using an immunological method; and (e) isolating the nucleic acid, where the isolated nucleic acid is a nucleic acid that binds a synMuv class C polypeptide. In another embodiment, further containing the following steps: (f) detectably labeling the nucleic acid of step (e); (g) contacting the detectably labeled nucleic acid with a microarray containing *C. elegans* nucleic acid fragments; and (h) detecting binding of the detectably labeled nucleic acid, where the binding identifies the nucleic acid as a nucleic acid target of a synMuv class C polypeptide.

By "binds" is meant a compound or antibody which recognizes and binds a polypeptide of the invention, but which does not substantially recognize and bind other different molecules in a sample, for example, a biological sample, which naturally includes a polypeptide of the invention.

By "cell" is meant a single-cellular organism, cell from a multi-cellular organism, or it may be a cell contained in a multi-cellular organism.

By "derived from" is meant isolated from or having the sequence of a naturally-occurring sequence (e.g., a cDNA, genomic DNA, synthetic, or combination thereof).

“Differentially expressed” means a difference in the expression level of a nucleic acid. This difference may be either an increase or a decrease in expression, when compared to control conditions.

By “*epc-1* nucleic acid” is meant a synMuv Class C nucleic acid
5 substantially identical to Y111B2A.11, which is identified by *C. elegans* cosmid name and open reading frame number.

By “EPC-1 polypeptide” is meant an amino acid sequence substantially identical to a polypeptide expressed by an *epc-1* nucleic acid that that functions in vulval development and associates with a MYST family histone
10 acetyltransferase.

By “fragment” is meant a portion of a protein or nucleic acid that is substantially identical to a reference protein or nucleic acid (e.g., one of those listed in Tables 2 or 3), and retains at least 50% or 75%, more preferably 80%, 90%, or 95%, or even 99% of the biological activity of the reference protein or
15 nucleic acid using a nematode bioassay as described herein or a standard biochemical or enzymatic assay.

By “hybridize” is meant pair to form a double-stranded molecule between complementary polynucleotide sequences (e.g., genes listed in Tables 1-4 and 7), or portions thereof, under various conditions of stringency. (See,
20 e.g., Wahl, G. M. and S. L. Berger (1987) *Methods Enzymol.* 152:399; Kimmel, A. R. (1987) *Methods Enzymol.* 152:507) For example, stringent salt concentration will ordinarily be less than about 750 mM NaCl and 75 mM trisodium citrate, preferably less than about 500 mM NaCl and 50 mM trisodium citrate, and most preferably less than about 250 mM NaCl and 25
25 mM trisodium citrate. Low stringency hybridization can be obtained in the absence of organic solvent, e.g., formamide, while high stringency hybridization can be obtained in the presence of at least about 35% formamide, and most preferably at least about 50% formamide. Stringent temperature conditions will ordinarily include temperatures of at least about 30°C, more
30 preferably of at least about 37°C, and most preferably of at least about 42°C.

Varying additional parameters, such as hybridization time, the concentration of detergent, e.g., sodium dodecyl sulfate (SDS), and the inclusion or exclusion of carrier DNA, are well known to those skilled in the art. Various levels of stringency are accomplished by combining these various conditions as needed.

5 In a preferred embodiment, hybridization will occur at 30°C in 750 mM NaCl, 75 mM trisodium citrate, and 1% SDS. In a more preferred embodiment, hybridization will occur at 37°C in 500 mM NaCl, 50 mM trisodium citrate, 1% SDS, 35% formamide, and 100 µg/ml denatured salmon sperm DNA (ssDNA). In a most preferred embodiment, hybridization will occur at 42°C in
10 250 mM NaCl, 25 mM trisodium citrate, 1% SDS, 50% formamide, and 200 µg/ml ssDNA. Useful variations on these conditions will be readily apparent to those skilled in the art.

For most applications, washing steps that follow hybridization will also vary in stringency. Wash stringency conditions can be defined by salt
15 concentration and by temperature. As above, wash stringency can be increased by decreasing salt concentration or by increasing temperature. For example, stringent salt concentration for the wash steps will preferably be less than about 30 mM NaCl and 3 mM trisodium citrate, and most preferably less than about 15 mM NaCl and 1.5 mM trisodium citrate. Stringent temperature conditions
20 for the wash steps will ordinarily include a temperature of at least about 25°C, more preferably of at least about 42°C, and most preferably of at least about 68°C. In a preferred embodiment, wash steps will occur at 25°C in 30 mM NaCl, 3 mM trisodium citrate, and 0.1% SDS. In a more preferred
25 embodiment, wash steps will occur at 42°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. In a most preferred embodiment, wash steps will occur at 68°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. Additional variations on these conditions will be readily apparent to those skilled in the art. Hybridization techniques are well known to those skilled in the art and are described, for example, in Benton and Davis (*Science* 196:180, 1977);
30 Grunstein and Hogness (*Proc. Natl. Acad. Sci., USA* 72:3961, 1975); Ausubel

et al. (*Current Protocols in Molecular Biology*, Wiley Interscience, New York, 2001); Berger and Kimmel (*Guide to Molecular Cloning Techniques*, 1987, Academic Press, New York); and Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, New York.

5 By "*hat-1* nucleic acid" is meant a a synMuv Class C nucleic acid substantially identical to VC5.4, which is identified by *C. elegans* cosmid name and open reading frame number.

By "HAT-1 polypeptide" is meant an amino acid sequence substantially identical to a polypeptide expressed by a *hat-1* nucleic acid that functions in
.. 10 . . vulval development and contains a chromodomain and an acetyltransferase catalytic domain.

By "*lin(n3628)* nucleic acid" is meant a nucleic acid substantially identical to SEQ ID NO:24 that encodes a histone methyltransferase.

By "LIN(n3628) polypeptide" is meant an amino acid sequence having
15 substantial identity to a polypeptide expressed by a *lin(n3628)* nucleic acid that has histone methyltransferase activity and includes a SET domain.

By "*lin(n4256)* nucleic acid" is meant a synMuv class B nucleic acid substantially identical to SEQ ID NO:27.

By "LIN(n4256) polypeptide" is meant an amino acid sequence having
20 substantial identity to a polypeptide expressed by a *lin(n4256)* nucleic acid and having histone methyltransferase activity.

By "*lin-65* nucleic acid" is meant a synMuv class B nucleic acid substantially identical to SEQ ID NO:28.

By "LIN-65 polypeptide" is meant an amino acid sequence having
25 substantial identity to a polypeptide expressed by a *lin-65* nucleic acid that is rich in acidic amino acids.

By "immunological assay" is meant an assay that relies on an immunological reaction, for example, antibody binding to an antigen. Examples of immunological assays include ELISAs, Western blots,
30 immunoprecipitations, and other assays known to the skilled artisan.

By "isolated polynucleotide" is meant a nucleic acid (e.g., a DNA) that is free of the genes which, in the naturally-occurring genome of the organism from which the nucleic acid molecule of the invention is derived, flank the gene. The term therefore includes, for example, a recombinant DNA that is incorporated into a vector; into an autonomously replicating plasmid or virus; or into the genomic DNA of a prokaryote or eukaryote; or that exists as a separate molecule (for example, a cDNA or a genomic or cDNA fragment produced by PCR or restriction endonuclease digestion) independent of other sequences. In addition, the term includes an RNA molecule that is transcribed from a DNA molecule, as well as a recombinant DNA that is part of a hybrid gene encoding additional polypeptide sequence.

By an "isolated polypeptide" is meant a polypeptide of the invention that has been separated from components that naturally accompany it. Typically, the polypeptide is isolated when it is at least 60%, by weight, free from the proteins and naturally-occurring organic molecules with which it is naturally associated. Preferably, the preparation is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight, a polypeptide of the invention. An isolated polypeptide of the invention may be obtained, for example, by extraction from a natural source, by expression of a recombinant nucleic acid encoding such a polypeptide; or by chemically synthesizing the protein. Purity can be measured by any appropriate method, for example, column chromatography, polyacrylamide gel electrophoresis, or by HPLC analysis.

By "KIAAA1732 nucleic acid" is meant a human nucleic acid sequence having substantial identity to SEQ ID NO:30 and encoding a histone methyltransferase.

By "KIAAA1732 polypeptide" is meant an amino acid sequence encoded by a nucleic acid substantially identical to SEQ ID NO:30, having histone methyltransferase activity, and including a SET domain.

By “*mep-1* nucleic acid” is meant a a synMuv Class B nucleic acid substantially identical to M04B2.1, which is identified by *C. elegans* cosmid name and open reading frame number.

By “MEP-1 polypeptide” is meant an amino acid sequence substantially identical to a polypeptide expressed by a *mep-1* nucleic acid that functions in vulval development and contains multiple Zn finger motifs.

By “multivulva” is meant having one vulva and one additional vulva-like structure.

By “nucleic acid” is meant an oligomer or polymer of ribonucleic acid or deoxyribonucleic acid, or analog thereof. This term includes oligomers consisting of naturally occurring bases, sugars, and intersugar (backbone) linkages as well as oligomers having non-naturally occurring portions which function similarly. Such modified or substituted oligonucleotides are often preferred over native forms because of properties such as, for example, enhanced cellular uptake and increased stability in the presence of nucleases.

Specific examples of some preferred nucleic acids envisioned for this invention may contain phosphorothioates, phosphotriesters, methyl phosphonates, short chain alkyl or cycloalkyl intersugar linkages or short chain heteroatomic or heterocyclic intersugar linkages. Most preferred are those with $\text{CH}_2\text{—NH—O—CH}_2$, $\text{CH}_2\text{—N(CH}_3\text{)—O—CH}_2$, $\text{CH}_2\text{—O—N(CH}_3\text{)—CH}_2$, $\text{CH}_2\text{—N(CH}_3\text{)—N(CH}_3\text{)—CH}_2$ and $\text{O—N(CH}_3\text{)—CH}_2\text{—CH}_2$ backbones (where phosphodiester is O—P—O—CH_2). Also preferred are oligonucleotides having morpholino backbone structures (Summerton, J.E. and Weller, D.D., U.S. Pat. No: 5,034,506). In other preferred embodiments, such as the protein-nucleic acid (PNA) backbone, the phosphodiester backbone of the oligonucleotide may be replaced with a polyamide backbone, the bases being bound directly or indirectly to the aza nitrogen atoms of the polyamide backbone (P.E. Nielsen et al. *Science* 199: 254, 1997). Other preferred oligonucleotides may contain alkyl and halogen-substituted sugar moieties comprising one of the following at the 2' position: OH, SH, SCH_3 , F, OCN,

O(CH₂)_nNH₂ or O(CH₂)_nCH₃, where n is from 1 to about 10; C₁ to C₁₀ lower alkyl, substituted lower alkyl, alkaryl or aralkyl; Cl; Br; CN; CF₃; OCF₃; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; SOCH₃; SO₂CH₃; ONO₂; NO₂; N₃; NH₂; heterocycloalkyl; heterocycloalkaryl; aminoalkylamino; polyalkylamino; substituted silyl; an RNA cleaving group; a conjugate; a reporter group; an intercalator; a group for improving the pharmacokinetic properties of an oligonucleotide; or a group for improving the pharmacodynamic properties of an oligonucleotide and other substituents having similar properties. Oligonucleotides may also have sugar mimetics such as cyclobutyls in place of the pentofuranosyl group.

Other preferred embodiments may include at least one modified base form. Some specific examples of such modified bases include 2-(amino)adenine, 2-(methylamino)adenine, 2-(imidazolylalkyl)adenine, 2-(aminoalkylamino)adenine, or other heterosubstituted alkyladenines.

By "ortholog" is meant a polypeptide or nucleic acid molecule of an organism that is highly related to a reference protein, or nucleic acid sequence, from another organism. An ortholog is functionally related to the reference protein or nucleic acid sequence. In other words, the ortholog and its reference molecule would be expected to fulfill similar, if not equivalent, functional roles in their respective organisms. It is not required that an ortholog, when aligned with a reference sequence, have a particular degree of amino acid sequence identity to the reference sequence. A protein ortholog might share significant amino acid sequence identity over the entire length of the protein, for example, or, alternatively, might share significant amino acid sequence identity over only a single functionally important domain of the protein. Such functionally important domains may be defined by genetic mutations or by structure-function assays. Orthologs may be identified using methods provided herein. The functional role of an ortholog may be assayed using methods well known to the skilled artisan, and described herein. For example, function might be assayed *in vivo* or *in vitro* using a biochemical, immunological, or enzymatic

assay; transformation rescue, or in a nematode bioassay for the effect of gene inactivation on nematode phenotype (e.g., fertility), as described herein.

Alternatively, bioassays may be carried out in tissue culture; function may also be assayed by gene inactivation (e.g., by RNAi, siRNA, or gene knockout), or
5 gene over-expression, as well as by other methods.

By “polypeptide” is meant any chain of amino acids, or analogs thereof, regardless of length or post-translational modification (for example, glycosylation or phosphorylation).

By “positioned for expression” is meant that the polynucleotide of the
10 invention (e.g., a DNA molecule) is positioned adjacent to a DNA sequence that directs transcription and translation of the sequence (i.e., facilitates the production of, for example, a recombinant polypeptide of the invention, or an RNA molecule).

By “purified antibody” is meant an antibody that is at least 60%, by
15 weight, free from proteins and naturally-occurring organic molecules with which it is naturally associated. Preferably, the preparation is at least 75%, more preferably 90%, and most preferably at least 99%, by weight, antibody. A purified antibody of the invention may be obtained, for example, by affinity chromatography using a recombinantly-produced polypeptide of the invention
20 and standard techniques.

By “specifically binds” is meant a compound or antibody that recognizes and binds a polypeptide of the invention, but which does not substantially recognize and bind other molecules in a sample, for example, a biological sample, which naturally includes a polypeptide of the invention.

By “*ssl-1* nucleic acid” is meant a nucleic acid substantially identical to
25 SEQ ID NO:21, which is identified by *C. elegans* cosmid name and open reading frame number.

By “SSL-1 polypeptide” is meant an amino acid sequence substantially identical to a polypeptide expressed by a *ssl-1* nucleic acid that functions in

embryonic development and has homology to p400 a SWI2/SNF2 family member having ATPase activity .

By “synthetic multivulva (synMuv) gene” is meant a gene that when mutated, interacts synergistically with a second synMuv gene to cause a synthetic multivulval phenotype. For example, *trr-1* and *mep-1* are synMuv genes because worms containing a mutation in *trr-1* or *mep-1*, and also having a mutation in *lin-15A* (e.g., *lin-15A(n767)*) display a synthetic multivulval phenotype.

By “*trr-1* nucleic acid” is meant a nucleic acid substantially identical to SEQ.ID.NO:12, which is identified by *C. elegans* cosmid name and open reading frame number. Nucleic acid and polypeptide sequence information is available at wormbase (www.wormbase.org), a central repository of data on *C. elegans*.

By “TRR-1 polypeptide” is meant an amino acid sequence substantially identical to a polypeptide expressed by a *trr-1* nucleic acid that functions in transcriptional regulation and vulval development.

“Therapeutic compound” means a substance that has the potential of affecting the function of an organism. Such a compound may be, for example, a naturally occurring, semi-synthetic, or synthetic agent. For example, the test compound may be a drug that targets a specific function of an organism. A test compound may also be an antibiotic or a nutrient. A therapeutic compound may decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of disease, disorder, or infection in a eukaryotic host organism.

The invention provides a number of targets that are useful for the development of highly specific drugs to treat neoplasia or a disorder characterized by the misregulation of the cell cycle (e.g., a hyperproliferative disorder). In addition, the methods of the invention provide a facile means to identify therapies that are safe for use in eukaryotic host organisms (i.e., compounds that do not adversely affect the normal development, physiology,

or fertility of the organism). In addition, the methods of the invention provide a route for analyzing virtually any number of compounds for effects on cell proliferation and cell cycle regulation with inexpensively and with high-volume throughput in a living animal.

5 Other features and advantages of the invention will be apparent from the detailed description, and from the claims.

The invention provides methods and compositions useful in treating a neoplasia and in identifying chemotherapeutic agents. Other features and advantages of the invention will be apparent from the detailed description, and
10 from the claims.

Brief Description of the Drawings

Figure 1A is a schematic diagram the location of *mep-1* on the LGIV physical map in between *sem-3* and *dpy-20*. The *mep-1* rescuing cosmid
15 M04B2 is shown in bold.

Figure 1B shows the predicted MEP-1 protein (SEQ ID NO:1). Zinc finger motifs are shaded, and the positions of *mep-1* mutations are indicated by arrowheads.

Figure 2 shows the genomic sequence of *mep-1* (SEQ ID NO:2). The
20 start and stop codons are indicated by highlighting.

Figure 3 shows the nucleic acid sequence of the *mep-1* open reading frame (SEQ ID NO:3).

Figure 4 shows the deduced amino acid sequence of MEP-1.

Figures 5A and 5B are bar graphs showing that *trr-1* single mutants are
25 defective in P(8).p fate specification. Induction of individual P(3-8).p cells was scored in wild-type animals (Figure 5A) and *trr-1(n3712)* mutants (Figure 5B). Certain cells in *trr-1* mutants adopted hybrid fates in which one of two Pn.p daughters divided like daughters of induced Pn.p cells and the other daughter remained undivided as in uninduced Pn.p cells. Ectopic induction in single

mutant animals containing each of the other five *trr-1* mutations was similarly restricted to P8.p.

Figure 6 is a bar graph showing that. *trr-1* and class B synMuv mutations are synthetically defective in P8.p cell-fate specification. P8.p induction was scored. We recognized *trr-1* homozygous mutants as non-Gfp progeny of *trr-1/ mIn1[dpy-10(e128) mIs14]* heterozygous parents. *lin-15B(n744)*, *lin-35(n745)*, *lin-36(n766)* and *lin-37(n758)* are the strongest mutations of their corresponding genes. Strains homozygous for these mutations are viable. *trr-1; synmuvB* double mutant strains with these mutations were derived from parents that were homozygous for the *synmuvB* mutation and hence lacked maternal and zygotic function of the class B synMuv gene in question. The *dpl-1(n3316)* null mutation causes sterility. We combined *dpl-1(RNAi)* with the *dpl-1(n3316)* mutation to generate mutants that lacked both maternal and zygotic *dpl-1* activity and recognized these mutants as non-Gfp progeny of *dpl-1(n3316) trr-1/ mIn1[dpy-10(e128) mIs14]* heterozygous parents that were injected with *dpl-1* dsRNA.

Figure 7A shows the *trr-1* gene structure as derived from cDNA and genomic sequences. Shaded boxes indicate coding sequence and open boxes indicate 5' and 3' untranslated regions. Predicted translation initiation and termination codons and the poly(A) tail are indicated. Positions of alternative splicing are indicated by asterisks. In all cases, the use of alternative splice acceptors creates small differences in the *trr-1* coding sequence: alternative splicings of the fourth (ag/TTTCAGAC (SEQ ID NO:4) versus agtttcag/AC (SEQ ID NO:5)), fifth (ag/AATCTTCAGTC (SEQ ID NO:6) versus (agaatcttcag/CC (SEQ ID NO:7)), eleventh (ag/AACTTTAAGAT (SEQ ID NO:8) versus agaactttaag/AT (SEQ ID NO:9) and twelfth introns (ag/TTGCAGAA (SEQ ID NO:10) versus agttgcag/AA (SEQ ID NO:11)) differ by either six or nine nucleotides.

Figure 7B is a schematic diagram of the TRR-1 protein. The positions of substitutions caused by TRR-1 mutations are indicated above. TRR-1 is

similar to mammalian TRRAP and yeast Tra1p throughout the lengths of the proteins. Domains of similarity (e.g., FAT and ATM/PI-3 kinase-like domains) that these three proteins share are indicated.

Figure 8 shows the genomic nucleic acid sequence of *trr-1* (SEQ ID NO:12). The start and stop codons are indicated by highlighting.

Figure 9 shows the nucleic acid sequence of the *trr-1* open reading frame (SEQ ID NO:13).

Figure 10 shows the deduced amino acid sequence of TRR-1 (SEQ ID NO:14).

Figure 11A is a schematic diagram showing the *hat-1* gene structure as derived from cDNA and genomic sequences. Shaded boxes indicate coding sequence and open boxes indicate 5' and 3' untranslated regions. Predicted translation initiation and termination codons and the poly(A) tail are shown.

Figure 11B is a schematic diagram of the HAT-1 protein. HAT-1 is similar to MYST family acetyltransferases, all of which contain a MOZ/SAS acetyltransferase domain and some of which contain a chromodomain. Nematodes expressing the *hat-1(n4075)* deletion are expected to produce only the first 35 amino acids of the wild-type HAT-1 protein and additional frameshifted amino acids prior to truncation.

Figure 11C is a bar graph showing that *hat-1* single mutants were defective in P(8).p fate specification. Induction of individual P(3-8).p cells was scored in wild-type animals (left) and *hat-1(n4075)* mutants (right). *hat-1* homozygous mutants were recognized as non-Unc progeny of *+/nT1n754*; *hat-1(n4075)/nT1n754* heterozygous parents.

Figure 11D is a bar graph showing that *hat-1* is synthetically defective in P8.p cell-fate specification with the class B synMuv mutation *lin-15B(n744)*. P8.p induction was scored as described below. *hat-1* homozygous mutants were recognized as in (C).

Figure 12 shows the genomic nucleic acid sequence of *hat-1* (SEQ ID NO:15). The start and stop codons are indicated by highlighting.

Figure 13 shows the nucleic acid sequence of the *hat-1* open reading frame (SEQ ID NO:16).

5 Figure 14 shows the deduced amino acid sequence of HAT-1 (SEQ ID NO:17).

Figure 15A is a schematic diagram showing *epc-1* and *ssl-1* gene structures and deletion mutations. The gene structure of *epc-1* was derived by comparing cDNA and genomic sequences.

10 Figure 15B is a schematic showing the *ssl-1* gene structure and deletion mutation. The gene structure of *ssl-1* is partially derived from comparison of cDNA and genomic sequences (SL1 splice leader, 5' untranslated region, exons 1-12 and the beginning of exon 13) and partially predicted solely from genomic sequence (the end of exon 13). As we do not have cDNA clones representing
15 the 3' end of *ssl-1*, we are unable to reliably assign a 3' untranslated region and poly(A) tail. Filled boxes indicate coding sequence and open boxes indicate 5' and 3' untranslated regions. SL1 splice leaders, predicted translation start and stop codons and poly(A) tail are shown. The regions of genomic sequence removed by the *epc-1*(n4076) and *ssl-1*(n4077) deletions are indicated.

20 Figure 16 shows the genomic nucleic acid sequence of *epc-1* (SEQ ID NO:18).

Figure 17 shows the nucleic acid sequence of the *epc-1* open reading frame (SEQ ID NO:19).

25 Figure 18 shows the deduced amino acid sequence of EPC-1 (SEQ ID NO:20).

Figure 19 shows the genomic nucleic acid sequence of *ssl-1* (SEQ ID NO:21) and the deduced amino acid sequence.

Figure 20A shows the exon boundaries of the *ssl-1* genomic nucleic acid sequence.

Figure 20B shows the cDNA nucleic acid sequence of *ssl-1* (SEQ ID NO:22).

Figure 21 shows the amino acid sequence of SSL-1 (SEQ ID NO:23).

Figures 22A and 22B are schematic diagrams showing two models of TRR-1/HAT-1/EPC-1 function with respect to class B synMuv proteins

Figure 22A is a schematic diagram showing that a TRR-1/HAT-1/EPC-1 complex and the class B synMuv proteins act on different targets and differentially regulate transcription. In this model a putative TRR-1/HAT-1/EPC-1 complex acts on targets that are different from those of a putative class B synMuv protein complex. A TRR-1/HAT-1/EPC-1 complex may promote transcription of genes that negatively regulate vulval development, whereas class B synMuv proteins may repress transcription of genes that promote vulval development.

Figure 22B is a schematic diagram showing a second model. In this second model, a TRR-1/HAT-1/EPC-1 complex acts on the same targets as do the class B synMuv proteins. Together these two putative protein complexes may specify an acetylation pattern on histones that is required for efficient silencing of genes that promote vulval development. A TRR-1/HAT-1/EPC-1 complex may act through DPL-1 and EFL-1, although genetic interactions suggest that not all TRR-1/HAT-1/EPC-1 complex activity goes through DPL-1 and EFL-1.

Figure 23 shows the genomic sequence of *lin(n3628)* including 1 kb of upstream and downstream genomic sequences (SEQ ID NO:24). The exon boundaries are also defined.

Figure 24 shows the amino acid sequence of LIN(n3628) (SEQ ID NO:25).

Figure 25 shows the genomic sequence of *lin(n4256)* (SEQ ID NO:26). The exon boundaries are also defined.

Figure 26 shows the amino acid sequence of LIN(n4256) (SEQ ID NO:27).

Figure 27 shows the genomic sequence of *lin-65* (SEQ ID NO:28). The exon boundaries are also defined.

Figure 28 shows the amino acid sequence of LIN-65 (SEQ ID NO:29). The exon boundaries are also defined.

5 Figure 29 shows the mRNA sequence that encodes the LIN(n3628) human ortholog, KIAA1732.

Figure 30 shows the amino acid sequence of KIAA1732 (SEQ ID NO:35).

10 Figure 31 defines the domains of LIN(n3628), including the SET catalytic domain.

Figure 33 defines the domains of KIAA1732, including the SET catalytic domain.

Description of the Invention

15 As reported in more detail below, we have identified new components of the Rb pathway that function in chromatin remodeling and antagonize Ras signaling, and methods for using such components for the identification of chemotherapeutics and the identification of new clinical targets for the treatment of neoplasia.

20

Example I

Isolation of new synMuv mutants

A variety of genetic studies revealed that sterility is often associated with a severe reduction of class B synMuv gene function. For example, in a genetic screen for alleles that did not complement the synMuv phenotype of *lin-9(n112)*, (Ferguson et al., *Genetics* 123: 109-21, 1989) recovered the alleles *lin-9(n942)* and *lin-9(n943)*, which caused sterility when homozygous. In another example, we performed gene dosage studies and observed that, in comparison to the wild-type *lin-52(n771)/Df* and *dpl-1(n2994)/Df* heterozygotes had markedly reduced brood sizes. In addition, deletion mutations of synMuv genes that showed recessive sterility were recovered by reverse genetic approaches (e.g. alleles of *lin-53* (LU 1999), *lin-54*, and *dpl-1* (Ceol et al., *Mol Cell* 7: 461-73, 2001).

Previous genetic screens for synMuv mutants (Ferguson et al., *Genetics* 123: 109-21, 1989) were performed before a link between loss of synMuv gene function and sterility was well established. These screens required that isolates be fertile and viable in order to recover mutant alleles. In addition to failing to recover recessive sterile mutations of the genes described above, these screens failed to recover mutations of the class B synMuv genes *efl-1* and *let-418*, both of which can mutate to a sterile phenotype (Von Zelewsky et al., *Development* 127: 5277-84, 2000; Ceol et al., *Mol Cell* 7: 461-73, 2001). Given this failure, we undertook a genetic screen to identify additional synMuv genes that would allow the recovery of homozygous sterile mutations through phenotypically wild-type heterozygous siblings.

To screen for new synMuv mutants, we examined the F₂ progeny of individually plated F₁ animals after EMS mutagenesis of *lin-15A(n767)* mutants. This screen represented 6760 haploid genomes examined for mutations that either alone or in combination with *lin-15A(n767)* showed a recessive Muv phenotype. Using this strategy we identified 95 Muv mutations, 24 of which were maintained as heterozygotes due to recessive sterility that

co-segregated with the Muv phenotype. Three mutations caused a Muv phenotype in the absence of *lin-15A*(n767) and were found to affect *lin-1* and *lin-31*, both of which function downstream of *let-60* Ras in vulval induction (Ferguson et al., *Nature* 326:259-67, 1987). These mutations, *lin-1*(n3443),
5 *lin-1*(n3522), and *lin-31*(n3440) were not characterized further. Additionally, we recovered 29 mutations that, together with *lin-15A*(n767), caused a weakly penetrant (< 30%) Muv phenotype. The remaining 63 mutations were assigned to 21 complementation groups, which include the previously known genes *ark-1*, *dpl-1*, *efl-1*, *gap-1*, *let-418*, *lin-9*, *lin-13*, *lin-15B*, *lin-35*, *lin-36*, *lin-52*,
10 *lin-53*, *lin-61*, and *sli-1*, and the new genes *lin*(n3441), *lin*(n3542), *lin*(n3628), *lin*(n3681), *lin*(n3707), *mep-1*, and *trr-1*.

Phenotypes of new mutants

We characterized the penetrance of the Muv phenotype for each strain at
15 15°C and 20°C. The results of this study are described in Table 1.

Table 1 Penetrance of Muv phenotype (n)

Genotype	15° C	20° C	Additional phenotypes
<i>ark-1(n3524) lin-15A(n767)</i>	0 (251)	80 (171)	
<i>ark-1(n3701); lin-15A(n767)</i>	12 (190)	95 (160)	
<i>dpl-1(n3643); lin-15A(n767)</i>	99 (154)	100 (252)	
<i>efl-1(n3639); lin-15A(n767)</i>	93 (74)	100 (78)	Ste
<i>gap-1(n3535) lin-15A(n767)</i>	1.4 (143)	50 (236)	
<i>let-418(n3536); lin-15A(n767)</i>	0 (201)	55 (183)	hs Ste
<i>let-418(n3626); lin-15A(n767)</i>	1.6 (62)	97 (76)	Ste
<i>let-418(n3629); lin-15A(n767)</i>	0 (52)	86 (58)	Ste
<i>let-418(n3634); lin-15A(n767)</i>	0 (87)	92 (48)	Ste
<i>let-418(n3635); lin-15A(n767)</i>	0 (76)	71 (70)	Ste
<i>let-418(n3636); lin-15A(n767)</i>	0 (77)	92 (78)	Ste
<i>let-418(n3719); lin-15A(n767)</i>	0 (101)	100 (60)	Ste
<i>lin-9(n3631); lin-15A(n767)</i>	100 (42)	100 (72)	Ste
<i>lin-9(n3675); lin-15A(n767)</i>	43 (166)	100 (105)	
<i>lin-9(n3767); lin-15A(n767)</i>	100 (67)	100 (56)	Ste
<i>lin-13(n3642); lin-15A(n767)</i>	3.3 (60)	100 (63)	Ste
<i>lin-13(n3673); lin-15A(n767)</i>	61 (145)	97 (129)	
<i>lin-13(n3674); lin-15A(n767)</i>	78 (131)	100 (191)	hs Ste
<i>lin-13(n3726); lin-15A(n767)</i>	31 (225)	99 (149)	hs Ste

Genotype	15° C	20° C	Additional phenotypes
<i>lin-15B(n3436) lin-15A(n767)</i>	100 (193)	100 (212)	
<i>lin-15B(n3676) lin-15A(n767)</i>	18 (167)	72 (130)	
<i>lin-15B(n3677) lin-15A(n767)</i>	99 (111)	100 (122)	
<i>lin-15B(n3711) lin-15A(n767)</i>	100 (186)	100 (156)	
<i>lin-15B(n3760) lin-15A(n767)</i>	32 (171)	100 (150)	
<i>lin-15B(n3762) lin-15A(n767)</i>	63 (113)	97 (116)	
<i>lin-15B(n3764) lin-15A(n767)</i>	96 (232)	100 (199)	
<i>lin-15B(n3766) lin-15A(n767)</i>	55 (132)	100 (173)	
<i>lin-15B(n3768) lin-15A(n767)</i>	80 (159)	100 (302)	
<i>lin-15B(n3772) lin-15A(n767)</i>	100 (220)	100 (191)	
<i>lin-35(n3438); lin-15A(n767)</i>	100 (153)	100 (126)	partial Ste at 20°C, Rup
<i>lin-35(n3763); lin-15A(n767)</i>	100 (108)	100 (160)	partial Ste at 20°C, Rup
<i>lin-36(n3671); lin-15A(n767)</i>	65 (191)	100 (151)	
<i>lin-36(n3672); lin-15A(n767)</i>	98 (198)	100 (178)	
<i>lin-36(n3765); lin-15A(n767)</i>	0 (184)	37 (202)	
<i>lin-52(n3718); lin-15A(n767)</i>	100 (41)	100 (82)	Ste
<i>lin-53(n3448); lin-15A(n767)</i>	67 (130)	100 (211)	partial Ste at 20°C

Genotype	15° C	20° C	Additional phenotypes
<i>lin-53(n3521); lin-15A(n767)</i>	100 (34)	100 (125)	partial Ste at 20°C
<i>lin-53(n3622); lin-15A(n767)</i>	85 (61)	100 (66)	Ste
<i>lin-53(n3623); lin-15A(n767)</i>	24 (55)	100 (51)	Ste
<i>lin-61(n3442); lin-15A(n767)</i>	22 (130)	100 (152)	
<i>lin-61(n3446); lin-15A(n767)</i>	36 (124)	99 (191)	
<i>lin-61(n3447); lin-15A(n767)</i>	11 (121)	87 (207)	
<i>lin-61(n3624); lin-15A(n767)</i>	0 (152)	89 (231)	
<i>lin-61(n3736); lin-15A(n767)</i>	0 (193)	100 (201)	
<i>n3441; lin-15A(n767)</i>	80 (165)	99 (195)	
<i>n3541; lin-15A(n767)</i>	79 (242)	98 (137)	
<i>n3543; lin-15A(n767)</i>	85 (177)	100 (121)	
<i>n3628; lin-15A(n767)</i>	2.9 (103)	84 (188)	
<i>n3681; lin-15A(n767)</i>	0 (214)	72 (192)	
<i>n3542 lin-15A(n767)</i>	0 (127)	35 (218)	
<i>n3707 lin-15A(n767)</i>	3.8 (80)	77 (26)	
<i>mep-1(n3680); lin-15A(n767)</i>	4.9 (122)	97 (105)	hs Ste
<i>mep-1(n3702); lin-15A(n767)</i>	30 (61)	100 (141)	Ste
<i>mep-1(n3703); lin-15A(n767)</i>	25 (72)	100 (107)	Ste
<i>sli-1(n3538) lin-15A(n767)</i>	4.3 (138)	90 (173)	
<i>sli-1(n3544) lin-15A(n767)</i>	4.6 (153)	80 (265)	cs embryonic lethality
<i>sli-1(n3683) lin-15A(n767)</i>	5.0 (80)	88 (148)	cs embryonic lethality
<i>trr-1(n3630); lin-15A(n767)</i>	3.1 (131)	85 (212)	Ste, Gro
<i>trr-1(n3637); lin-15A(n767)</i>	1.1 (92)	80 (200)	Ste, Gro

Genotype	15° C	20° C	Additional phenotypes
<i>trr-1(n3704); lin-15A(n767)</i>	3.1 (96)	79 (244)	Ste, Gro
<i>trr-1(n3708); lin-15A(n767)</i>	2.0 (151)	84 (228)	Ste, Gro
<i>trr-1(n3709); lin-15A(n767)</i>	1.0 (97)	77 (154)	Ste, Gro
<i>trr-1(n3712); lin-15A(n767)</i>	5.8 (121)	77 (192)	Ste, Gro

Ste: sterile; Gro: growth rate abnormal; Rup: rupture at the vulva; cs: cold sensitive; hs: heat sensitive.

The penetrance of the Muv phenotype was determined after growing synMuv mutant strains at the indicated temperature for two or more generations. For most strains in which a fully penetrant sterile phenotype was associated with the Muv phenotype, we scored the penetrance of the Muv phenotype by examining sterile progeny of heterozygous mutant parents. For *trr-1* mutant strains, we scored the penetrance of the Muv phenotype by examining non-Gfp progeny of *trr-1 / mIn1[dpy-10(e128)mIs14]; lin-15A(n767)* heterozygous parents. All strains were backcrossed to *lin-15A(n767)* twice prior to phenotypic characterization. In addition to the phenotypes described above, many of the strains exhibited heat sensitive inviability due to frequent rupture, sterility, and/or general sickness.

The penetrance at 25°C is not shown because all strains had a highly penetrant (>90%) Muv phenotype at this temperature. Since a heat-sensitive Muv phenotype is characteristic of most synMuv strains, including those with null mutations in synMuv genes (Ferguson et al., *Genetics* 123: 109-21, 1989), it is likely that many synMuv mutations are not particularly temperature sensitive, but rather that the synMuv genes regulate a temperature sensitive process.

A subset of our synMuv strains also exhibited a sterile phenotype. In these strains, the sterile phenotype cosegregated with the Muv phenotype during backcrosses and two- and three-factor mapping experiments. For those mutations tested, we found that our new mutations did not complement the sterile phenotypes caused by previously isolated, allelic synMuv mutations. These observations suggest that the sterile and Muv phenotypes of these strains were caused by the same mutation.

We observed an unusual aspect to the sterility of one of our strains. We examined the *mep-1(n3680); lin-15A(n767)* strain and found that its sterile phenotype showed maternal-effect rescue. When derived from heterozygous parents, the sterility of the *mep-1(n3680); lin-15A(n767)* animals was 3.2% penetrant (n=62), but was 55% penetrant (n=69) when these animals were derived from homozygous parents. Mutations that affect the Mes (Mes, maternal-effect sterility) genes also show maternal-effect rescue of sterility (Capowski et al., *Genetics* 129: 1061-72, 1991). Some Mes genes encode homologs of *Drosophila* polycomb group proteins and are proposed to function in X chromosome transcriptional silencing in the germline (Holdeman et al., *Development* 125: 2457-67, 1998; Korf et al., *Development* 125: 2469-78, 1998; Fong et al., *Science* 296: 2235-8, 2002). A functional relationship between the synMuv and Mes genes has not been previously reported.

15 New synMuv genes

Using two-factor crosses and sex chromosome transmission tests, we mapped the new mutations to linkage groups (Table 2).

Table 2 Chromosomal linkages of new synMuv mutations**A. Autosomal mutations**

New mutation	Mutation used for selection of homozygous F₂ hermaphrodites	Genotype of selected F₂ hermaphrodites with respect to the linked, unselected mutation
<i>ark-1(n3524)</i>	<i>dpy-20(e1282) IV</i>	2/19 <i>ark-1(n3524)/+</i>
<i>ark-1(n3701)</i>	<i>ark-1(n3701)</i>	1/14 <i>dpy-20(e1282)/+ IV</i>
<i>dpl-1(n3643)</i>	<i>dpl-1(n3643)</i>	0/20 <i>rol-6(e187)/+ II</i>
<i>efl-1(n3639)</i>	<i>rol-4(sc8) V</i>	4/20 <i>efl-1(n3639)/+</i>
<i>let-418(n3536)</i>	<i>let-418(n3536)</i>	4/21 <i>rol-4(sc8)/+ V</i>
<i>let-418(n3626)</i>	<i>rol-4(sc8) V</i>	0/19 <i>let-418(n3626)/+</i>
<i>let-418(n3629)</i>	<i>rol-4(sc8) V</i>	1/20 <i>let-418(n3629)/+</i>
<i>let-418(n3634)</i>	<i>rol-4(sc8) V</i>	2/19 <i>let-418(n3634)/+</i>
<i>let-418(n3635)</i>	<i>rol-4(sc8) V</i>	5/20 <i>let-418(n3635)/+</i>
<i>let-418(n3636)</i>	<i>rol-4(sc8) V</i>	3/20 <i>let-418(n3636)/+</i>
<i>let-418(n3719)</i>	<i>rol-4(sc8) V</i>	2/30 <i>let-418(n3719)/+</i>
<i>lin-9(n3631)</i>	<i>unc-32(e189) III</i>	0/20 <i>lin-9(n3631)/+</i>
<i>lin-9(n3675)</i>	<i>lin-9(n3675)</i>	0/22 <i>unc-32(e189)/+ III</i>
<i>lin-9(n3767)</i>	<i>lin-9(n3767)</i>	0/16 <i>mgP21/+ III</i>
<i>lin-13(n3642)</i>	<i>unc-32(e189) III</i>	1/20 <i>lin-13(n3642)/+</i>
<i>lin-13(n3673)</i>	<i>lin-13(n3673)</i>	0/25 <i>unc-32(e189)/+ III</i>
<i>lin-13(n3674)</i>	<i>lin-13(n3674)</i>	0/25 <i>unc-32(e189)/+ III</i>
<i>lin-13(n3726)</i>	<i>lin-13(n3726)</i>	1/26 <i>unc-32(e189)/+ III</i>
<i>lin-35(n3438)</i>	<i>lin-35(n3438)</i>	0/30 <i>dpy-5(e61)/+ I</i>
<i>lin-35(n3763)</i>	<i>lin-35(n3763)</i>	0/22 <i>dpy-5(e61)/+ I</i>
<i>lin-36(n3671)</i>	<i>lin-36(n3671)</i>	1/23 <i>unc-32(e189)/+ III</i>
<i>lin-36(n3672)</i>	<i>lin-36(n3672)</i>	0/16 <i>unc-32(e189)/+ III</i>
<i>lin-36(n3765)</i>	<i>lin-36(n3765)</i>	0/9 <i>unc-32(e189)/+ III</i>
<i>lin-52(n3718)</i>	<i>lin-52(n3718)</i>	1/16 <i>mgP21/+ III</i>
<i>lin-53(n3448)</i>	<i>lin-53(n3448)</i>	1/22 <i>dpy-5(e61)/+ I</i>
<i>lin-53(n3521)</i>	<i>dpy-5(e61) I</i>	0/20 <i>lin-53(n3521)/+</i>
<i>lin-53(n3622)</i>	<i>dpy-5(e61) I</i>	5/30 <i>lin-53(n3622)/+</i>
<i>lin-53(n3623)</i>	<i>lin-53(n3623)</i>	4/16 <i>hP4/+ I</i>
<i>lin-61(n3442)</i>	<i>lin-61(n3442)</i>	0/20 <i>dpy-5(e61)/+ I</i>
<i>lin-61(n3446)</i>	<i>lin-61(n3446)</i>	1/23 <i>dpy-5/+ I</i>

New mutation	Mutation used for selection of homozygous F ₂ hermaphrodites	Genotype of selected F ₂ hermaphrodites with respect to the linked, unselected mutation
<i>lin-61(n3447)</i>	<i>lin-61(n3447)</i>	0/13 <i>dpy-5(e61)/+ I</i>
<i>lin-61(n3624)</i>	<i>lin-61(n3624)</i>	0/15 <i>dpy-5(e61)/+ I</i>
<i>lin-61(n3736)</i>	<i>dpy-5(e61) I</i>	1/19 <i>lin-61(n3736)/+</i>
<i>lin(n3441)</i>	<i>lin(n3441)</i>	5/20 <i>dpy-5(e61)/+ I</i>
<i>lin(n3541)</i>	<i>lin(n3541)</i>	9/31 <i>dpy-5(e61)/+ I</i>
<i>lin(n3543)</i>	<i>lin(n3543)</i>	9/27 <i>dpy-5(e61)/+ I</i>
<i>lin(n3628)</i>	<i>lin(n3628)</i>	1/29 <i>dpy-5(e61)/+ I</i>
<i>lin(n3681)</i>	<i>lin(n3681)</i>	3/22 <i>rol-4(sc8)/+ V</i>
<i>mep-1(n3680)</i>	<i>mep-1(n3680)</i>	0/30 <i>dpy-20(e1282)/+, IV</i>
<i>mep-1(n3702)</i>	<i>mep-1(n3702)</i>	0/16 <i>sP4/+ IV</i>
<i>mep-1(n3703)</i>	<i>mep-1(n3703)</i>	0/16 <i>sP4/+ IV</i>
<i>trr-1(n3630)</i>	<i>rol-6(e187) II</i>	0/20 <i>trr-1(n3630)/+</i>
<i>trr-1(n3637)</i>	<i>rol-6(e187) II</i>	1/20 <i>trr-1(n3637)/+</i>
<i>trr-1(n3704)</i>	<i>rol-6(e187) II</i>	1/30 <i>trr-1(n3704)/+</i>
<i>trr-1(n3708)</i>	<i>rol-6(e187) II</i>	0/20 <i>trr-1(n3708)/+</i>
<i>trr-1(n3709)</i>	<i>rol-6(e187) II</i>	2/30 <i>trr-1(n3709)/+</i>
<i>trr-1(n3712)</i>	<i>rol-6(e187) II</i>	1/19 <i>trr-1(n3712)/+</i>

B. X-linked mutations

New mutation	Criteria for X linkage
<i>lin(n3542)</i>	transmission test
<i>lin(n3707)</i>	transmission test
<i>gap-1(n3535)</i>	transmission test
<i>lin-15B(n3436)</i>	males with pseudovulva
<i>lin-15B(n3676)</i>	transmission test, males with pseudovulva
<i>lin-15B(n3677)</i>	males with pseudovulva
<i>lin-15B(n3711)</i>	males with pseudovulva
<i>lin-15B(n3760)</i>	transmission test, males with pseudovulva
<i>lin-15B(n3762)</i>	males with pseudovulva
<i>lin-15B(n3764)</i>	transmission test, males with pseudovulva
<i>lin-15B(n3766)</i>	transmission test, males with pseudovulva
<i>lin-15B(n3768)</i>	transmission test, males with pseudovulva
<i>lin-15B(n3772)</i>	transmission test, males with pseudovulva
<i>sli-1(n3538)</i>	transmission test
<i>sli-1(n3544)</i>	transmission test
<i>sli-1(n3683)</i>	transmission test

Autosomal and sex chromosome linkages were determined as described below. *lin(n3541)* was also mapped relative to *bli-3(e767)* and *unc-54(e1092)*, mutations present on the extreme left and right arms, respectively, of linkage group I. Of 16 Muv progeny selected from a *lin(n3541) / bli-3(e767) unc-54(e1092); lin-15A(n767)* parent, none were *bli-3(e767)/+* whereas six were *unc-54(e1092)/+*, indicating *lin(n3541)* lies nearer to *bli-3(e767)*.

We then determined if a given mutation failed to complement mutations of known synMuv genes on the same linkage group. Mutations that were not assigned to known synMuv complementation groups were tested against unassigned mutations within the same linkage group for complementation. These tests defined seven new synMuv loci: *trr-1*, *mep-1*, *lin(n3441)*, *lin(n3628)*, *lin(n3681)*, *lin(n3707)*, and *lin(n3542)*. We used three-factor

crosses to map most of these new synMuv genes within their respective linkage groups (Table 3).

Table 3 Map data for newly-identified synMuv loci

5

A. Three- and four-factor mapping

Gene	Genotype of heterozygote	Phenotype of selected recombinants	Genotype of selected recombinants (with respect to unselected markers)
<i>ark-1</i>	+ + <i>ark-1</i> / <i>unc-5 dpy-20</i> +; <i>lin-15A</i> (n767)	Unc	10/10 <i>ark-1</i> / +
		Dpy	0/1 <i>ark-1</i> / +
	+ <i>ark-1</i> + / <i>dpy-20</i> + <i>unc-30</i> ; <i>lin-15A</i> (n767)	Dpy	15/35 <i>ark-1</i> / +
		Unc	17/33 <i>ark-1</i> / +
	<i>dpy-20</i> + + <i>ark-1</i> / + <i>lin-3 unc-22</i> +; <i>lin-15A</i> (n767)	Dpy	3/9 <i>unc-22</i> / +
		Muv	3/3 <i>unc-22</i> / +
	<i>dpy-20</i> + <i>ark-1</i> + / + <i>unc-22</i> + <i>unc-30</i> ; <i>lin-15A</i> (n767)	Dpy	1/3 <i>unc-22</i> / +
		Muv	1/2 <i>unc-22</i> / +
		Unc-22	2/3 <i>ark-1</i> / +
		Unc-30	5/6 <i>ark-1</i> / +
	<i>dpy-20</i> + <i>ark-1</i> + / + <i>dpy-26</i> + <i>unc-30</i> ; <i>lin-15A</i> (n767)	Dpy-20	4/7 <i>dpy-26</i> / +
		Muv	3/8 <i>dpy-26</i> / +
<i>gap-1</i>	+ + <i>gap-1 lin-15A</i> (n767) / <i>unc-1 dpy-3</i> + <i>lin-15A</i> (n767)	Unc	17/17 <i>gap-1</i> / +
		Dpy	0/8 <i>gap-1</i> / +
	<i>gap-1</i> + + <i>lin-15A</i> (n767) / + <i>unc-2 lon-2 lin-15A</i> (n767)	Unc	0/2 <i>gap-1</i> / +
		Lon	6/6 <i>gap-1</i> / +
<i>lin-52</i>	+ <i>gap-1</i> + <i>lin-15A</i> (n767) / <i>dpy-3</i> + <i>unc-2 lin-15A</i> (n767)	Unc	14/18 <i>gap-1</i> / +

Gene	Genotype of heterozygote	Phenotype of selected recombinants	Genotype of selected recombinants (with respect to unselected markers)
	<i>+ lin-52 + / unc-16 + unc-47; lin-15A(n767)</i>	Unc-47	7/9 <i>lin-52 / +</i>
	<i>lin-52 + unc-69 / + stP127 +; lin-15A(n767)</i>	Muv	3/12 <i>stP127 / +</i>
	<i>sma-3 + lin-52 + / + sqv-3 + unc-69; lin-15A(n767)</i>	Sma	9/9 <i>sqv-3 / +</i>
		Muv	1/27 <i>sqv-3 / +</i>
		Unc	14/16 <i>lin-52 / +</i>
<i>lin(n3441)</i>	<i>+ lin(n3441) + / bli-3 + lin-17; lin-15A(n767)</i>	Lin-17	9/19 <i>lin(n3441) / +</i>
	<i>bli-3 + lin(n3441) / + spe-15 +; lin-15A(n767)</i>	Muv	10/18 <i>spe-15 / +</i>
	<i>+ lin(n3441) lin-17 / spe-15 + +; lin-15A(n767)</i>	Lin-17	11/11 <i>spe-15 / +</i>
<i>lin(n3628)</i>	<i>lin(n3628) + + / + dpy-5 unc-13; lin-15A(n767)</i>	Dpy	0/6 <i>lin(n3628) / +</i>
		Unc	6/6 <i>lin(n3628) / +</i>
	<i>+ lin(n3628) + / unc-11 + dpy-5; lin-15A(n767)</i>	Unc	1/11 <i>lin(n3628) / +</i>
		Dpy	5/11 <i>lin(n3628) / +</i>
	<i>unc-11 + + lin(n3628) / + unc-73 lin-44 +; lin-15A(n767)</i>	Muv	3/9 <i>unc-73 lin-44 / + +</i>
	<i>+ + lin(n3628) dpy-5 / unc-73 lin-44 + +; lin-15A(n767)</i>	Muv	0/21 <i>unc-73 lin-44 / + +</i>
	<i>lin(n3628) + dpy-5 / + unc-38 +; lin-15A(n767)</i>	Muv	3/7 <i>unc-38 / +</i>
	<i>unc-11 lin(n3628) + / + + unc-38; lin-15A(n767)</i>	Muv	0/9 <i>unc-38 / +</i>
<i>lin(n3542)</i>	<i>+ + + lin(n3542) lin-15A(n767) / unc-10 dpy-6 lin-15A(n767)</i>	Unc	8/8 <i>lin(n3542) / +</i>
	<i>+ lin(n3542) + lin-15A(n767) / dpy-6 + unc-9 lin-15A(n767)</i>	Unc	4/40 <i>lin(n3542) / +</i>
<i>mep-1</i>	<i>+ mep-1 + / unc-5 + dpy-20; lin-15A(n767)</i>	Unc	56/57 <i>mep-1 / +</i>
		Dpy	2/61 <i>mep-1 / +</i>
	<i>mep-1 + + / + dpy-20 unc-30; lin-15A(n767)</i>	Dpy	0/51 <i>mep-1 / +</i>
		Unc	58/58 <i>mep-1 / +</i>
	<i>+ + mep-1 + / unc-24 mec-3 + dpy-20; lin-15A(n767)</i>	UncMec	10/12 <i>mep-1 / +</i>

Gene	Genotype of heterozygote	Phenotype of selected recombinants	Genotype of selected recombinants (with respect to unselected markers)
		Unc	17/17 <i>mep-1</i> / +
		MecDpy	0/8 <i>mep-1</i> / +
		Dpy	2/8 <i>mep-1</i> / +
	+ <i>mep-1 dpy-20</i> + / <i>lin-3</i> + + <i>unc-22</i> ; <i>lin-15A(n767)</i>	Dpy	5/5 <i>lin-3</i> / +
		Vul	3/10 <i>mep-1</i> / +
	+ + <i>mep-1</i> + / <i>mec-3 sem-3</i> + <i>dpy-20</i> ; <i>lin-15A(n767)</i>	Mec	17/17 <i>mep-1</i> / +
		Dpy	6/13 <i>mep-1</i> / +
<i>sli-1</i>	<i>sli-1</i> + + <i>lin-15A(n767)</i> / + <i>lon-2 unc-6 lin-15A(n767)</i>	Lon	0/6 <i>sli-1</i> / +
	<i>sli-1</i> + + <i>lin-15A(n767)</i> / + <i>unc-2 lon-2 lin-15A(n767)</i>	Lon	5/5 <i>sli-1</i> / +
	<i>sli-1</i> + + <i>lin-15A(n767)</i> / + <i>dpy-3 unc-2 lin-15A(n767)</i>	Dpy	0/10 <i>sli-1</i> / +
		Unc	6/6 <i>sli-1</i> / +
	<i>sli-1</i> + + <i>lin-15A(n767)</i> / + <i>unc-1 dpy-3 lin-15A(n767)</i>	Unc	0/14 <i>sli-1</i> / +
		Dpy	10/10 <i>sli-1</i> / +
<i>trr-1</i>	+ <i>rol-6</i> + <i>trr-1</i> / <i>dpy-10</i> + <i>unc-4</i> +; <i>lin-15A(n767)</i>	Rol	3/14 <i>unc-4</i> / +
		Dpy	3/3 <i>trr-1</i> / +
		Unc	0/8 <i>trr-1</i> / +
	+ <i>trr-1</i> + / <i>dpy-10</i> + <i>rol-1</i> ; <i>lin-15A(n767)</i>	Rol	9/20 <i>trr-1</i> / +
	+ + <i>trr-1</i> / <i>dpy-10 unc-53</i> +; <i>lin-15A(n767)</i>	Unc	0/17 <i>trr-1</i> / +
	+ <i>trr-1</i> + / <i>unc-53</i> + <i>rol-1</i> ; <i>lin-15A(n767)</i>	Unc	7/10 <i>trr-1</i> / +
		Rol	7/10 <i>trr-1</i> / +
	+ <i>trr-1</i> + <i>rol-1</i> / <i>unc-4</i> + <i>mex-1</i> +; <i>lin-15A(n767)</i>	Rol	12/14 <i>mex-1</i> / +

B. Deficiency mapping

Gene	Genotype of heterozygote	Phenotype of heterozygote
<i>lin-52</i>		

	<i>unc-36 lin-52 / nDf40 dpy-18; lin-15A(n767)</i>	Muv
<i>mep-1</i>	<i>mep-1 / sDf63 unc-31; lin-15A(n767) / +</i>	PvlSte
	<i>mep-1 / sDf62 unc-31; lin-15A(n767) / +</i>	PvlSte
	<i>mep-1 / sDf10; lin-15A(n767) / +</i>	WT
<i>trr-1</i>	<i>rol-6 trr-1 / mnDf57; lin-15A(n767)</i>	WT
	<i>rol-6 trr-1 / unc-4 mnDf90; lin-15A(n767)</i>	WT
	<i>rol-6 trr-1 / mnDf29; lin-15A(n767)</i>	WT
	<i>trr-1 / unc-4 mnDf87; lin-15A(n767)</i>	Muv

WT: wild-type; Pvl: protruding vulva; Ste: sterile.

Three- and four-factor crosses were performed using standard methods (Brenner, *Genetics* 77: 71-94, 1974). Deficiency heterozygotes were constructed as described below. In addition, we have isolated *trr-1*, *mep-1*, *lin(n3628)*, and *lin(n3681)* mutations away from the parental *lin-15A(n767)* mutation. *mep-1*, *lin(n3628)*, and *lin(n3681)* mutations alone do not cause a Muv phenotype, and *trr-1* mutations alone cause only weak ectopic vulval induction. Thus, these mutations synergize with *lin-15A(n767)* and are indeed synMuv mutations.

We identified mutations in *gap-1* and *sli-1*, two genes that were originally identified in screens for mutations that suppressed the Vul phenotype caused by a reduction in *let-60* Ras pathway signaling (Jongeward et al., *Genetics* 139: 1553-66, 1995; Hajnal et al., *Genes Dev* 11: 2715-28, 1997). We also identified mutations in *ark-1*, a gene that was first identified in a screen for mutations that caused ectopic vulval induction in a *sli-1* mutant background (Hopper et al., *Mol Cell* 6: 65-75, 2000). *gap-1*, *sli-1*, and *ark-1* single mutants were previously isolated and found to have no (*sli-1*, *gap-1*) or subtle (*ark-1*) defects in vulval development. Our results indicate that *sli-1*, *gap-1*, and *ark-1* act redundantly with *lin-15A* to negatively regulate *let-60* Ras signaling.

Molecular identification of *mep-1*

We isolated three mutations, *n3680*, *n3702* and *n3703*, in a gene that we mapped to a small interval on linkage group IV in between *sem-3* and *dpy-20* as shown in Figure 1. We attempted to rescue the Muv phenotype of *n3680*; *lin-15A(n767)* mutants using cosmid clones from this interval. Transgenic animals containing the cosmid M04B2 were rescued for the Muv phenotype and also showed improved fertility relative to non-transgenic animals. The genomic sequence of *mep-1* is shown in Figure 2. The *mep-1* open reading frame sequence is shown in Figure 3. This gene was originally identified based on its interaction with the germline specification genes *mog-1*, *mog-4*, *mog-5* and *pie-1* in yeast two-hybrid screens (Belfiore et al. RNA. 8:725-39, 2002). Because somatic tissues adopt germ cell-specific characteristics in *mep-1* mutants, *mep-1* is thought to repress germ cell fates in the soma. We sequenced *mep-1* in our mutant strains to determine if the mutations we isolated affected this gene. These mutations identify functionally important amino acid residues or domains. *n3680* mutants have a missense mutation that, in the predicted MEP-1 protein, changes a polar serine residue to an asparagine. *n3702* mutants have a nonsense mutation and *n3703* mutants a splice acceptor mutation in the *mep-1* gene. Our genetic mapping data, cosmid rescue, and DNA sequence results indicate that *n3680*, *n3702*, and *n3703* are *mep-1* mutations.

The deduced amino acid sequence of MEP-1 is shown in Figure 4. *mep-1* encodes a protein containing six zinc-finger motifs. Zinc fingers are known to mediate interactions of proteins with DNA and with other proteins. The zinc fingers of MEP-1 likely mediate interactions with LET-418 or other synMuv proteins.

Sequences of synMuv mutations

We determined sequences of mutations that affected additional synMuv genes (Table 4).

Table 4 Selected synMuv proteins and allele sequences**A. Features of selected synMuv proteins**

Protein	No. amino acids	Protein similarities and domains
DPL-1	598	Similar to DP family transcription factors; Contains DNA- and E2F-binding domains
EFL-1	342	Similar to E2F family transcription factors; Contains DNA-binding, DP-binding and transactivation domains
LET-418	1829	Similar to Mi-2 family ATP-dependent chromatin remodeling enzymes; Contains chromodomains, PHD finger motifs and a helicase domain*
LIN-9	LIN-9L: 644 LIN-9S: 642	Similar to <i>Drosophila</i> Aly cell cycle regulator and mammalian proteins of unknown function
LIN-13	2248	Protein has 24 Zn-finger motifs
LIN-35	961	Similar to Retinoblastoma (pRb) family transcriptional regulators; Contains "pocket" interaction domain
LIN-36	962	Novel protein with C/H-rich and Q-rich regions
LIN-52	161	Similar to <i>Drosophila</i> and mammalian proteins of unknown function
LIN-53	417	Similar to <i>Drosophila</i> p55, mammalian RbAp48 subunits of chromatin remodeling and histone deacetylase complexes; Contains WD repeats
LIN-61	491	Similar to <i>Drosophila</i> l(3)mbt and other MBT repeat-containing proteins
MEP-1	853	Protein has six Zn finger motifs
SLI-1	582	Similar to Cbl family ubiquitination-promoting proteins; Contains SH2 domain and RING finger motif
TRR-1	4064 [†]	Similar to mammalian TRRAP transcriptional regulator

B. Allele sequences

Mutation	Wild-type sequence	Mutant sequence	Substitution, splice site change or aberration	Domain affected by missense mutation
<i>dpl-1</i> (n3643)	TAT	TAA	Y341ochre	-
<i>efl-1</i> (n3639)	CAA	TAA	Q175ochre	-
<i>let-</i> <i>418</i> (n3536)	CCT	CTT	P675L	helicase/ATPase
<i>let-</i> <i>418</i> (n3626)	GGT	AGT	G1006S	helicase/ATPase
<i>let-</i> <i>418</i> (n3629)	TCC	TTC	S925F	helicase/ATPase
<i>let-</i> <i>418</i> (n3634)	TGG	TAG	W1128amber	-
<i>let-</i> <i>418</i> (n3635)	CAG	TAG	Q1594amber	-
<i>let-</i> <i>418</i> (n3636)	ACT	ICT	T807S	helicase/ATPase
<i>let-</i> <i>418</i> (n3719)	TGG	TAG	W295amber	-
<i>lin-9</i> (n3631)	CAA	TAA	LIN-9L: Q594ochre	-
<i>lin-9</i> (n3675)	GAT	AAT	LIN-9S: Q592ochre	-
<i>lin-9</i> (n3767)	CAG	TAG	LIN-9L: D305N	none predicted
<i>lin-</i> <i>13</i> (n3642)	CAT	TAT	LIN-9S: D303N	none predicted
<i>lin-</i> <i>13</i> (n3673)	CAG	TAG	LIN-9L: Q509amber	-
<i>lin-</i> <i>13</i> (n3674)	CGA	TGA	LIN-9S: Q507amber	-
<i>lin-</i> <i>13</i> (n3726)	GGA	GAA	H832Y	Zn finger
			Q1988amber	-
			R1250opal	-
			G229E	none predicted

Mutation	Wild-type sequence	Mutant sequence	Substitution, splice site change or aberration	Domain affected by missense mutation
<i>lin-</i> 35(n3763) ^o	<u>G</u> CA	<u>G</u> TA	A555V	Pocket
	TTG AAA	TTG AAA	K594frameshift and	
	AAG	AAA G	truncation after 611a.a.	-
<i>lin-</i> 36(n3671)	<u>C</u> AT	<u>C</u> CT	H284P	C/H-rich region
	<u>G</u> AA	<u>A</u> AA	E424K	none predicted
<i>lin-</i> 36(n3672)	<u>C</u> AG	<u>T</u> AG	Q467amber	-
<i>lin-</i> 36(n3765) [†]	<u>G</u> CT	<u>G</u> TT	A242V	C/H-rich region
<i>lin-</i> 52(n3718)	<u>C</u> AG	<u>T</u> AG	Q31amber	-
<i>lin-</i> 53(n3448)	<u>A</u> GT	<u>A</u> TT	S384I	WD repeat
<i>lin-</i> 53(n3521)	<u>G</u> AA	<u>A</u> AA	E174K	WD repeat
		AAG/atatgtgt		
<i>lin-</i> 53(n3622)	AAG/gtatgtgt	(SEQ ID NO:30)	Exon 1 donor	-
<i>lin-</i> 53(n3623)	<u>T</u> GG	<u>T</u> AG	W337amber	-
		aacttcag/AAT		
<i>lin-</i> 61(n3442)	aacttcag/AAT	(SEQ ID NO:31)	Exon 4 acceptor	-
<i>lin-</i> 61(n3446)	<u>C</u> AA	<u>T</u> AA	Q412ochre	-
<i>lin-</i> 61(n3447)	<u>A</u> GT	<u>A</u> AT	S354N	MBT repeat
<i>lin-</i> 61(n3624)	<u>C</u> CG	<u>T</u> CG	P132S	none predicted

Mutation	Wild-type sequence	Mutant sequence	Substitution, splice site change or aberration	Domain affected by missense mutation
<i>lin-</i> 61(n3736)	<u>TTT</u>	<u>TCT</u>	F247S	MBT repeat
<i>mep-</i> 1(n3680)	<u>AGT</u>	<u>AAT</u>	S309N	none predicted
<i>mep-</i> 1(n3702)	<u>CAG</u>	<u>TAG</u> CTT/ataagttt (SEQ ID	Q706amber	-
<i>mep-</i> -1(n3703)	CTT/gtaagttt	NO:32)	Exon 3 donor	-
<i>sli-1</i> (n3538)	<u>TCA</u>	<u>TTA</u> ttttccaa/AAA (SEQ ID	S305L	SH2
<i>sli-1</i> (n3544)	ttttccag/AAA	NO:33) tttttaa/GAT (SEQ ID	Exon 6 acceptor	-
<i>sli-1</i> (n3683)	tttttag/GAT	NO:34)	Exon 4 acceptor	-
<i>trr-1</i> (n3630)	<u>TGG</u>	<u>TAG</u>	W2064amber	-
<i>trr-1</i> (n3637)	<u>CAG</u>	<u>TAG</u>	Q3444amber	-
<i>trr-1</i> (n3704)	<u>CAA</u>	<u>TAA</u>	Q694ochre	-
<i>trr-1</i> (n3708)	<u>CGA</u>	<u>TGA</u>	R1248opal	-
<i>trr-1</i> (n3709)	<u>CGA</u>	<u>TGA</u>	R2550opal	-
<i>trr-1</i> (n3712)	<u>TGG</u>	<u>TAG</u>	W2505amber	-

In the "Wild-type sequence" and "Mutant sequence" columns, exon and intron sequences are denoted by uppercase and lowercase script, respectively. Nucleotides altered by mutation are underlined.

5 * The predicted LET-418 protein contains a sequence described as a helicase domain. This domain was originally identified in helicases, but has since been found in non-helicase proteins. Many of these proteins share a common ATPase activity, and this domain contains residues that are important for ATP binding and hydrolysis.

† The adenosine inserted by the *lin-35*(n3763) frameshift mutation is not underlined because it is unclear which nucleotide in the adenosine repeat was inserted.

10 ‡ In addition to the missense mutation described, we found an additional mutation associated with *lin-36*(n3765). This mutation, AG/gtaagaagaaaagc to AG/gtaagaagaaaagt, is present in the third intron of *lin-36* and creates a possible splice donor sequence. If this splice donor were used, an inframe ochre (TAA) stop codon would be encountered, truncating the LIN-36 protein after 261 amino acids.

15 § Due to alternative splicing, *trr-1* encodes proteins that range in length between 4051 and 4061 amino acids

DPL-1 and EFL-1 are described by (Ceol et al., *Mol Cell* 7: 461-73, 2001 and (Page et al., *Mol Cell* 7: 451-60, 2001). LIN-9 is described by Beitel et al., *Gene* 254: 253-63, 2000); LIN-13 is

described by Melendez et al., *Genetics* 155: 1127-37, 2000); LIN-35 and LIN-53 are described by (Lu et al., *Cell* 95:981-91, 1998); LIN-36 is described by (Thomas et al., *Development* 126: 3449-59, 1999); and SLI-1 is described by (Yoon et al., *Science* 269: 1102-5, 1995).

5 Most mutations are GC-to-AT transitions that are characteristic of EMS mutagenesis (Anderson, *Methods Cell Biol* pp. 31-58, 1995). Many of these mutations are predicted to truncate the corresponding synMuv proteins. The truncations predicted by *efl-1(n3639)*, *let-418(n3719)*, and *lin-52(n3718)* are particularly severe, and the synMuv and sterile phenotypes caused by these
10 mutations may represent the null phenotypes of these genes. In addition, we found missense mutations that disrupt predicted functional domains of synMuv proteins. For example, *n3536*, *n3626*, *n3629* and one of the two mutations of *n3636* affect the ATPase/helicase domain of LET-418. LET-418 is a member of the Mi-2 family of ATP-dependent chromatin remodeling enzymes (Solari et al.,
15 *Curr Biol* 10: 223-6, 2000; Von Zelewsky et al., *Development* 127: 5277-84, 2000), and the LET-418 missense mutations suggest that LET-418 function is similarly dependent on ATP hydrolysis. At least one mutation affecting the LIN-13 protein, *n3642*, is predicted to disrupt a canonical zinc-finger motif. This missense mutation indicates that at least some of the twenty-four LIN-13
20 zinc fingers are important for its synMuv activity. Missense mutations affecting other synMuv proteins are not as easily linked to the disruption of predicted functional domains. These mutations may provide a useful starting point in identifying functional motifs within synMuv proteins that are not predicted by sequence comparisons.

25

Frequency of mutant isolation

The rate at which we isolated mutations was much higher than that observed in previous synMuv screens: including those 63 mutations described in this study, we recovered one synMuv mutation per 107 haploid genomes
30 screened versus 1/750 (Ferguson et al., *Genetics* 123: 109-21, 1989), 1/400 and 1/667 in previous screens. We believe the reasons for this difference are threefold. First, our screen design allowed the isolation of synMuv mutations

that also caused sterility. Sterile synMuv mutants were observed previously, but because the heterozygous siblings of these mutants were present in a sea of genotypically unrelated animals, the underlying mutations could not be recovered. Second, our parental strain carried the strong class A mutation, *lin-15A(n767)*. The penetrance of a strain's Muv phenotype is dependent on the aggregate strengths of the component synMuv mutations. Therefore, even weak mutations may be identified in a strong synMuv background such as *lin-15A(n767)*. Although we have not formally tested this possibility, we believe that some of the mutations we recovered only weakly affect synMuv activity. Such mutations may not have been recovered in previous screens that were performed in partial loss-of-function synMuv backgrounds. Third, in screening a plate of many F₂ progeny derived from a single F₁ animal, we observed many genotypically identical animals per haploid genome screened. This type of screening likely accounts for our isolation of a number of partially penetrant synMuv mutations. Such mutations may not have been identified in earlier synMuv screens that typically observed fewer genotypically identical animals per haploid genome screened.

Our high rate of recovery indicates many genes can mutate to a synMuv phenotype. Including the ten genes we identified in this study, a total of 25 genes can act redundantly with class A synMuv genes. Many of these genes are represented by one or a few mutant alleles, indicating that screens for synMuv genes are not saturated.

The synMuv genes we identified likely act in different pathways

Class B synMuv mutations synergize with class A synMuv mutations, but not with other class B synMuv mutations. Such genetic behavior led to the hypothesis that class B synMuv genes are part of a single genetic pathway (Ferguson et al., *Genetics* 123:109-21, 1989). In support of this hypothesis, mutations affecting different class B synMuv genes are similarly suppressed by loss-of-function mutations in the *let-23* receptor tyrosine kinase and other

let-60 Ras pathway loss-of-function mutations (Ferguson et al., *Nature* 326:259-67, 1987), a subset of class B synMuv gene products have been shown to interact *in vitro*, and their homologs are known function together in other systems (Lu et al., *Cell* 95: 981-91, 1998; Ceol et al., *Mol Cell* 7: 461-73, 2001). Because we conducted our screen in a class A synMuv background, we anticipated recovering mutations that affected genes of the class B synMuv pathway. In addition to Class B synMuv mutations, our results suggest that we recovered mutations that disable distinct genetic pathways. We recovered six mutations that affect the *trr-1* gene. Unlike typical class B synMuv mutations, *trr-1(n3712)* synergize not only with class A synMuv mutations, but also with class B synMuv mutations. *trr-1(n3712)* single mutants also atypically show ectopic vulval induction. Because of its unusual genetic interactions, we propose that *trr-1* functions in a pathway distinct from the class B synMuv pathway. We also recovered mutations affecting the *sli-1*, *gap-1*, and *ark-1* genes. These genes were previously characterized as negative regulators of *let-60* Ras pathway activity, acting genetically downstream of the *let-23* receptor tyrosine kinase (Jongeward et al., *Genetics* 139: 1553-66, 1995; Hajnal, et al., *Genes Dev* 11: 2715-28 1997; Hopper et al., *Mol Cell* 6: 65-75, 2000). The molecular identities of *sli-1*, *gap-1*, and *ark-1* support their action downstream of *let-23*. *sli-1* encodes a homolog of the c-cbl proto-oncoprotein, which is thought to downregulate receptor tyrosine kinase levels through ubiquitin-mediated degradation (Yoon et al., *Science* 269: 1102-5, 1995; Levkowitz et al., *Mol Cell* 4: 1029-40, 1999). *gap-1* is a member of the GTPase-activating protein family (Hajnal, et al., *Genes Dev* 11: 2715-28 1997). GAPs enhance the catalytic function of Ras family GTPases, thereby facilitating the switch from active GTP-bound to inactive GDP-bound Ras. *ark-1* encodes a predicted cytoplasmic tyrosine kinase that interacts with the SEM-5 SH2/SH3 adaptor protein (Hopper et al., *Mol Cell* 6: 65-75, 2000). Since *sem-5* acts downstream of the *let-23* receptor tyrosine kinase, *ark-1* is proposed to inhibit *let-60* Ras signaling downstream of *let-23*. These genetic

and molecular data suggest that *sli-1*, *gap-1*, and *ark-1* directly regulate *let-60* Ras pathway members and are likely not part of the canonical class B synMuv pathway, which is thought to regulate the *let-60* Ras pathway either upstream of, or in parallel to, the *let-23* receptor tyrosine kinase. We are currently
5 placing our synMuv mutations into different genetic classes by examining interactions with class B synMuv and *let-23* mutations.

***lin-52* encodes a new putative Rb pathway protein**

lin-35, a member of the class B synMuv pathway, encodes a protein
10 similar to the mammalian tumor suppressor pRb (Lu et al., *Cell* 95: 981-91, 1998). Other genes with class B synMuv activity encode DP, E2F, RbAp48, histone deacetylase and HP1 family proteins (Lu et al., *Cell* 95: 981-91, 1998; Ceol et al., *Mol Cell*, 7: 461-73, 2001; Couteau et al., *EMBO Rep* 3: 235-41, 2002). Mammalian homologs of these proteins are known to functionally, and
15 in some cases physically, interact with pRb. These and other parallels indicate that the class B synMuv pathway is an analog of Rb pathways in other systems. Consequently, additional class B synMuv genes may have homologs with analogous functions in other systems. One such gene is *lin-52*. By the genetic criteria outlined above, *lin-52* is a class B synMuv gene. *lin-52* mutations
20 synthetically interact with class A mutations, but not with class B mutations. Furthermore, preliminary experiments indicate that the Vul phenotype of a *let-23* loss-of-function mutation is epistatic to the Muv phenotype caused by *lin-52* and *lin-15A* loss of function. *lin-52* encodes a small protein, portions of which are conserved in similarly small proteins predicted by the human, mouse
25 and *Drosophila* genome sequences. The characterization of these and other class B synMuv protein homologs should help to determine whether they too function in Rb-mediated signaling.

The experiments described above were carried out as follows

Strains and general techniques

- Strains were cultured as described by (Brenner, *Genetics* 77: 71-94, 1974). and grown at 20°C unless otherwise indicated. The wild-type parent of all the strains described in this study was the *Caenorhabditis elegans* Bristol strain N2. For some two and three-factor mapping experiments we used the polymorphic strain RW7000 (Williams et al., *Genetics* 131: 609-24, 1992). We also used strains containing the following mutations:
- LGI: *bli-3(e767)*, *lin-17(n677)*, *unc-11(e47)*, *unc-73(e936)*, *lin-44(n1792)*,
 10 *unc-38(x20)*, *dpy-5(e61)*, *lin-35(n745)*, *lin-61(sy223)*, *unc-13(e1091)*,
lin-53(n833) (Ferguson et al., *Genetics* 123: 109-21 (1989), *unc-54(e1092)* (Dibb et al., *J. Mol Biol* 183: 543-51, 1985).
- LGII: *lin-31(n301)*, *dpy-10(e128)*, *tra-2(q276)*, *rol-6(e187)*, *dpl-1(n2994)*,
unc-4(e120), *unc-53(n569)*, *mex-1(it9)*, *rol-1(e91)*
- 15 LGIII: *dpy-17(e164)*, *lon-1(e185)*, *sma-3(e491)*, *lin-13(n770)* (Ferguson et al., *Genetics* 123: 109-21 (1989), *lin-37(n758)*, *lin-36(n766)*, *unc-36(e251)*,
lin-9(n112), *unc-32(e189)*, *unc-16(e109)*, *sqv-3(n2842)*, *lin-52(n771)* (Ferguson et al., *Genetics* 123: 109-21 (1989), *unc-47(e307)*, *unc-69(e587)*,
dpy-18(e364)
- 20 LGIV: *lin-1(e1275)*, *unc-5(e53)*, *unc-24(e138)*, *mec-3(e1338)*, *lin-3(n378)*,
sem-3(n1900), *dpy-20(e1282)*, *unc-22(e66)*, *dpy-26(n198)*, *unc-31(e169)*,
unc-30(e191), *lin-54(n2231)*, *dpy-4(e1166)* LGV: *tam-1(cc567)* (Hsieh et al., *Genes Dev* 13: 2958-70, 1999), *unc-46(e177)*, *let-418(s1617)*, *dpy-11(e224)*,
rol-4(sc8), *unc-76(e911)*, *efl-1(n3318)* Ceol et al., *Mol Cell* 7: 461-73 (2001).
- 25 *dpy-21(e428)* LGX: *sli-1(sy143)*, *aex-3(ad418)*, *unc-1(e1598n1201)*,
dpy-3(e27), *gap-1(gal33)* (Hajnal et al., *Genes Dev* 11: 2715-28, 1997),
unc-2(e55), *lon-2(e678)*, *unc-10(e102)*, *dpy-6(e14)*, *unc-9(e101)*, *unc-3(e151)*,
lin-15A(n767), *lin-15AB(n765)*. Unless otherwise noted, the mutations used are described by (Riddle et al., *C. elegans II* (Cold Spring Harbor, New York, Cold Spring Harbor Laboratory Press 1997). In addition, we used strains
- 30

containing the following chromosomal aberrations: *mnDf57 II* (Sigurdson, et al., *Genetics* 108: 331-45, 1984), *mnDf90 II* (Sigurdson, et al., *Genetics* 108: 331-45, 1984), *mnDf29 II* (Sigurdson, et al., *Genetics* 108: 331-45, 1984), *mnDf87 II* (Sigurdson, et al., *Genetics* 108: 331-45, 1984),

5 *mIn1[dpy-10(e128)mIs14] II* (Edgley et al., *Mol Genet Genomics* 266: 385-95, 2001), *mnC1[dpy-10(e128) unc-52(e444)] II* (Herman, *Genetics* 88: 49-65, 1978), *nDf40 III* (Hengartner et al., *Nature* 356: 494-9, 1992), *qC1[dpy-19(e1259)glp-1(q339)] III* (Austin, et al., *Cell* 58: 565-571, 1989), *sDf63 IV*, *sDf62 IV* (Clark et al., *Mol Gen Genet* 232: 97-105, 1992), *sDf10 IV*

10 (Rogalski et al., *Genetics* 102: 725-36, 1982), *eT1(III;V)* (Rosenbluth et al., *Genetics* 99: 415-28, 1981), *nT1(IV;V)* (Ferguson et al., *Genetics* 110: 17-72, 1985). *mIs14*, an integrated transgene linked to the chromosomal inversion *mIn1*, consists of a combination of GFP-expressing transgenes that allow

15 *mIs14*-containing animals to be scored beginning at the 4-cell stage of embryogenesis (Edgley et al., *Mol Genet Genomics* 266: 385-95, 2001).

Isolation of new alleles

We mutagenized *lin-15A(n767)* hermaphrodites with ethyl methanesulfonate (EMS) as described by (Brenner, *Genetics* 77: 71-94, 1974).

20 We allowed these animals to recover on food for between 15 minutes to one hour, and then transferred individual P₀ larvae in L4 lethargus to 50 mm plates. After three to five days, 20 F₁ L4 larvae per P₀ were individually transferred to 50 mm plates, and, subsequently, F₂ animals on these plates were screened for a Muv phenotype. We screened the progeny of 3380 F₁ animals using this

25 procedure.

Linkage group assignment

We used the following markers to determine linkage of newly isolated synMuv mutations to autosomes: *dpy-5 I*, *rol-6 II*, *unc-32 III*, *dpy-20 IV*, *rol-4*

30 *V*. We generated animals heterozygous for the new synMuv mutation and for

at least two of these markers. For fertile synMuv mutants we picked Muv progeny and determined if these progeny segregated the markers, whereas for sterile synMuv mutants we picked single marker homozygotes and determined if these animals segregated the synMuv mutation. We also mapped some mutations using polymorphisms present in the RW7000 strain. We generated animals heterozygous for the new synMuv mutation and for RW7000 markers. We picked individual Muv progeny of these animals, performed lysis and used the resulting template DNA to monitor linkage to each of the autosomes by PCR (Williams et al., *Genetics* 131: 609-24, 1992). We tested for sex linkage to assign some new synMuv mutations to the X chromosome. Briefly, we generated heterozygous or hemizygous mutant males and mated them with marked *lin-15A(n767)* hermaphrodites. We then determined whether all, indicating sex linkage, or roughly half, indicating autosomal linkage, of the cross progeny hermaphrodites of this mating segregated the synMuv mutation. Some *lin-15B* mutations were not tested for sex linkage. Instead, we tentatively assigned X-chromosome linkage based on the presence, when *lin-15A(n767)* males were mated with these mutants, of cross-progeny males with pseudovulval ventral protrusions. Such protrusions are often observed in hemizygous *lin-15AB* mutant males (Ferguson et al., *Genetics* 110: 17-72, 1985) but are found at a much lower penetrance in *lin-15A(n767)* males that are hemizygous for an X-linked synMuv mutation affecting genes other than *lin-15B*. The mutations we assigned in this manner were later determined by complementation tests to affect *lin-15B*.

25 Complementation tests

We typically performed complementation tests by mating males heterozygous for the new mutation and hemizygous for *lin-15A(n767)*, or, if X-linked, males hemizygous for both the new mutation and *lin-15A(n767)*, into marked synMuv mutant hermaphrodites, all of which contained a *lin-15A* mutation. Hemizygous *lin-15B(n3711)lin-15A(n767)* males could not mate.

To perform complementation tests with this mutation, we mated *tra-2(q276); lin-15B(n3711)lin-15A(n767)/++* XX males into marked *lin-15AB* hermaphrodites. For new mutations that caused recessive sterility, we generated heterozygous males by starting matings with wild-type L4 males and individual gravid, putative heterozygous mutant hermaphrodites. For complementation tests we used cross-progeny males derived from plates that had self-progeny Muv animals present. In all complementation tests, unmarked cross-progeny hermaphrodites were scored.

10 Construction of deficiency heterozygotes.

To construct *trr-1(n3712)* heterozygotes with *mnDf57*, *mnDf90* and *mnDf29*, *Df/mIn1*; *lin-15A(n767)* males were generated. These males were mated into *rol-6 trr-1(n3712)/mIn1*; *lin-15A(n767)* hermaphrodites and non-Rol, non-Gfp cross-progeny were scored. *mnDf87* heterozygous males do not mate so in this case we generated *lin(n3712)/mnDf87*; *lin-15A(n767)* animals by mating *lin(n3712)/mIn1*; *lin-15A(n767)* males into *unc-4 mnDf87/mIn1*; *lin-15A(n767)* hermaphrodites. To construct the *lin-52* heterozygote with *nDf40*, we mated *nDf40 dpy-18/unc-36*; *lin-15A(n767)* males into *unc-36 lin-52(n771)*; *lin-15A(n767)* hermaphrodites and scored non-Unc cross-progeny. *mep-1/Df* animals were constructed by mating *Df/nT1*; *+/nT1* males into *dpy-20 mep-1*; *lin-15A(n767)* hermaphrodites and scoring non-Dpy cross-progeny.

Transgenic animals

25 Germline transformation was performed, as described by (Mello et al., *Embo J* 10: 3959-70, 1991), by injecting cosmid (5-10 ng/ μ L) or plasmid (50-80 ng/ μ L) DNA into *lin-52* or *mep-1* mutants. Either pRF4, which causes a dominant Rol phenotype, or pPD93.97, which expresses *gfp* under the control of the *myo-3* promoter, was used as a coinjection marker.

30

***lin-52* cDNA isolation**

We obtained a partial *lin-52* cDNA clone, yk253b12, that included 249 nucleotides of the *lin-52* open reading frame and also included the 3' untranslated region and a polyA tail. We used the 5' RACE system v2.0 for rapid amplification of chromosome ends (GIBCO-BRL, LIFE TECHNOLOGIES, Inc. Gaithersburg, Maryland) to determine the 5' end of the *lin-52* transcript. We ligated the two portions of the *lin-52* cDNA together to generate a full-length cDNA clone. The *lin-52* 5' RACE products were *trans-spliced* to the SL2 leader sequence consistent with observations made by (Zorio et al., *Nature* 372: 270-2, 1994).

Allele sequence

We used PCR-amplified regions of genomic DNA as templates in determining gene sequences. For each gene investigated, we determined the sequences of all exons and splice junctions. Whenever observed, the sequence of a mutation was confirmed using an independently-derived PCR product. All sequences were determined using an automated ABI 373 DNA sequencer.

Example II

As detailed below, we have identified a distinct class of genes, termed the class C synMuv genes, that negatively regulate vulval induction.

Proper vulval development in the nematode *C. elegans* requires that specific ectodermal cells, termed Pn.p cells, adopt different cell fates. The specification of Pn.p cells that eventually make vulval tissue occurs in two steps, each of which involves the selection of a subset of Pn.p cells from a larger Pn.p field (Sulston, *Dev Biol* 56: 110-56, 1977). In the first step, which occurs in the L1 larval stage shortly after the Pn.p cells are generated, anterior and posterior Pn.p cells fuse with the syncytial hypodermis. After this first step, the unfused midbody P(3-8).p cells each have the capacity to adopt a vulval cell fate (Sternberg et al., *Cell* 44: 761-72, 1986). In a second step,

however, only three of these cells, P(5-7).p, adopt such fates in which they undergo three rounds of division to generate seven or eight descendants. P3.p, P4.p and P8.p adopt non-vulval fates, typically dividing only once to generate two descendants that eventually fuse with the syncytial hypodermis. The decision to adopt vulval cell fates occurs during the L2 and early L3 larval stages and is followed by cell divisions and differentiation in the L3 and L4 larval stages, respectively (Sternberg et al., *Cell* 44: 761-72, 1986; Ferguson et al., *Nature* 326: 259-67, 1987). While mutations in class C synMuv genes alone cause mild defects, when a class C gene mutation is combined with either a class A or class B mutation, the two mutations synergize to produce more severe vulval induction and other developmental defects. Class C synMuv genes, *trr-1*, *hat-1*, and *epc-1*, encode homologs of the transcriptional coactivator TRRAP, the MYST family acetyltransferases TIP60 and Esa1p and the *Drosophila* Enhancer of Polycomb (E(Pc)) protein, respectively. Because of the predicted acetyltransferase activity of the HAT-1 protein and because orthologs TRRAP and E(Pc) family proteins have been copurified in histone acetyltransferase complexes, we propose that a combination of histone acetyltransferase and histone deacetylase activities is required to properly specify vulval cell fates in *C. elegans*.

20

***trr-1* interacts with class A and class B synMuv mutations**

We performed a genetic screen for synMuv mutants in a *lin-15A(n767)* background and identified six mutations in our pool of isolates that failed to complement each other and that defined the gene *trr-1*. To quantitate the synMuv phenotype in these mutants, we scored the number of cells that were induced to become vulva.

To more precisely quantitate the Muv phenotype of *trr-1; lin-15A* strains, we scored the numbers of P(3-8).p cells induced per animal and found that all strains had a similarly penetrant, temperature-sensitive hyperinduced phenotype (Table 5A).

30

Table 5 *trr-1* mutations cause a hyperinduced phenotype

A. <i>trr-1</i> interactions with synMuv mutations				
Genotype	Temp (°C)	Ave. # P(3-8).p induced (\pm SE)	% animals hyperinduced	n
wild-type	20	3.00 (\pm 0)	0	31
<i>lin-15A</i> (n767)	20	3.00 (\pm 0)	0	24
<i>lin-38</i> (n751)	20	3.00 (\pm 0)	0	27
<i>trr-1</i> (n3630); <i>lin-15A</i> (n767)	20	4.52 (\pm 0.15)	82	45
<i>trr-1</i> (n3637); <i>lin-15A</i> (n767)	20	4.52 (\pm 0.14)	83	54
<i>trr-1</i> (n3704); <i>lin-15A</i> (n767)	20	4.20 (\pm 0.13)	79	43
<i>trr-1</i> (n3708); <i>lin-15A</i> (n767)	20	4.71 (\pm 0.14)	92	36
<i>trr-1</i> (n3709); <i>lin-15A</i> (n767)	20	4.81 (\pm 0.13)	95	39
<i>trr-1</i> (n3712); <i>lin-15A</i> (n767)	20	4.07 (\pm 0.12)	74	54
<i>lin-15A</i> (n767); <i>trr-1</i> (RNAi)	20	5.60 (\pm 0.08)	100	44
<i>trr-1</i> (n3712) <i>lin-38</i> (n751)	20	4.14 (\pm 0.23)	79	14
<i>lin-38</i> (n751); <i>trr-1</i> (RNAi)	20	5.66 (\pm 0.08)	100	32
wild-type	15	3.00 (\pm 0)	0	29
<i>lin-15A</i> (n767)	15	3.00 (\pm 0)	0	32
<i>trr-1</i> (n3704); <i>lin-15A</i> (n767)	15	3.13 (\pm 0.05)	21	24
<i>trr-1</i> (n3712); <i>lin-15A</i> (n767)	15	3.06 (\pm 0.03)	13	32
wild-type	25	3.00 (\pm 0)	0	36
<i>lin-15A</i> (n767)	25	3.02 (\pm 0.02)	3.6	28
<i>trr-1</i> (n3704); <i>lin-15A</i> (n767)	25	5.87 (\pm 0.06)	100	38
<i>trr-1</i> (n3712); <i>lin-15A</i> (n767)	25	5.47 (\pm 0.14)	100	17

B. *trr-1* single mutants

Genotype	Temp (°C)	Ave. # P(3-8).p induced (\pm SE)	% animals	
			hyperinduced	n
wild-type	20	3.00 (\pm 0)	0	31
<i>trr-1</i> (n3630)	20	3.03 (\pm 0.02)	6.1	33
<i>trr-1</i> (n3637)	20	3.08 (\pm 0.04)	13	30
<i>trr-1</i> (n3704)	20	3.01 (\pm 0.01)	2.6	39
<i>trr-1</i> (n3708)	20	3.05 (\pm 0.03)	8.1	37
<i>trr-1</i> (n3709)	20	3.03 (\pm 0.02)	6.3	32
<i>trr-1</i> (n3712)	20	3.10 (\pm 0.03)	13	89
<i>trr-1</i> (RNAi)	20	3.09 (\pm 0.05)	13	32
wild-type	15	3.00 (\pm 0)	0	29
<i>trr-1</i> (n3704)	15	3.08 (\pm 0.05)	12	26
<i>trr-1</i> (n3712)	15	3.06 (\pm 0.03)	12	25
wild-type	25	3.00 (\pm 0)	0	36
<i>trr-1</i> (n3704)	25	3.04 (\pm 0.03)	3.9	51
<i>trr-1</i> (n3712)	25	3.07 (\pm 0.03)	13	48

The number of P(3-8).p cells induced was scored as described below.

Induction was scored after raising strains at the indicated temperature for two generations. *trr-1* mutant homozygotes were scored by examining the non-Gfp progeny of *trr-1/mIn1[dpy-10(e128) mIs14]* heterozygous parents.

The hyperinduction we observed occurred in P3.p, P4.p and P8.p to similar extents. To determine if *trr-1* interacted with other class A synMuv genes, we constructed a *trr-1*(n3712) *lin-38* double mutant. These double mutant animals were also hyperinduced (Table 5A), suggesting that *trr-1* functions in parallel not only to *lin-15A*, but to the class A synMuv pathway in general.

We also isolated *trr-1*(n3712) and the other *trr-1* mutations away from any other synMuv mutations. Nearly all class A and class B synMuv single mutants adopt a wild-type pattern of P(3-8).p fates (Table 5B), however *trr-1* adults had a weakly penetrant hyperinduced phenotype (Table 5B). By

examining the cell fates adopted by individual P(3-8).p cells in L4 animals, we determined that the vulval cell-fate transformations of *trr-1* single mutants always occurred in P8.p (Figure 5). In addition to ectopic vulval cell-fate transformations, all *trr-1* mutations caused slow growth and sterility, although
5 some mutant animals occasionally produced a small number of eggs (<10, as compared to ~300 for the wild-type), all of which died during embryogenesis.

To determine if *trr-1* interacts with class B synMuv genes, we constructed double mutant strains containing *trr-1(n3712)* and mutations of class B synMuv genes. Interestingly, double mutant strains combining
10 *trr-1(n3712)* with mutations of *lin-15B*, *lin-35* Rb, and *lin-37* showed a significant increase in the penetrance of P8.p transformation (Figure 6). In addition to the increase in P8.p transformation, we occasionally observed ectopic transformations of P3.p and P4.p. Since *lin-15B(n744)*, *lin-35(n745)* and *lin-37(n758)* are strong loss-of-function and possibly null mutations of
15 their corresponding genes, these results indicate that *trr-1* functions redundantly with at least a subset of class B synMuv genes.

No significant increase was observed in *trr-1(n3712); lin-36(n766)* double mutants (Figure 6). By various genetic criteria, this loss-of-function *lin-36* mutation behaves unlike mutations in other class B synMuv genes
20 (Hsieh et al., *Genes Dev* 13: 2958-70, 1999; Fay et al., *Genes Dev* 16: 503-17, 2002). There are at least two possibilities to explain the unusual behavior of *lin-36(n766)*. First, the lack of enhancement could be allele specific, with the *lin-36(n766)* mutation disrupting a function that is redundant with a class A synMuv function but not disrupting a separable *lin-36* function that is
25 redundant with *trr-1* activity. Alternatively, our observations with *lin-36* could reflect a gene-specific lack of enhancement. For example, the strength of the *lin-36* defect may not be equivalent to that of other class B synMuv gene defects such that lack of *lin-36* activity may be readily observable in a class A synMuv background but, unlike other class B synMuv defects, not observable

in a *trr-1* background. Enhancement tests using additional *lin-36* alleles will help to resolve this issue.

***trr-1* encodes a protein similar to mammalian TRRAP**

5 We mapped *trr-1* to a small region of LGII and cloned the gene using transformation rescue as detailed below. To confirm the identity of *trr-1*, we obtained a partial cDNA and, using RNA derived from this cDNA, found that RNA-mediated interference (RNAi) of this gene caused a highly penetrant hyperinduced phenotype in *lin-15A* and *lin-38* mutant backgrounds (Table 5).
10 As determined by RT-PCR and 5' RACE, the *trr-1* gene consists of 22 exons, four of which are alternatively spliced (Figure 7A). Since the sites of alternative splicing are separated by only six or nine nucleotides, the most exclusive (4054 amino acids) and inclusive (4064 amino acids) isoforms differ slightly in size. The genomic sequence of *trr-1* is shown in Figure 8. The
15 sequence of the *trr-1* open reading frame is shown in Figure 9.

 The deduced amino acid sequence of TRR-1 is shown in Figure 10. The predicted TRR-1 proteins are similar to mammalian myc-associated protein TRRAP (transformation/transcription domain-associated protein) and its yeast homolog Tra1p throughout most of their lengths (McMahon et al., *Cell* 94:
20 363-74, 1998; McMahon et al., *Cell* 94: 363-74, 1998; Saleh et al., *J Biol Chem* 273: 26559-65, 1998). TRRAP and Tra1p are similarly large proteins, extending 3828 and 3744 amino acids, respectively. The largest predicted TRR-1 isoform is 25 percent identical to TRRAP and 19 percent identical to Tra1p. TRR-1, TRRAP, and Tra1p share limited regions of homology with
25 other proteins (Figure 7B). One of these regions is located at the carboxy terminus and is similar to the catalytic domains of ATM and PI-3-like kinases. Interestingly, the DXXXXN (SEQ ID NO:29) and DFG motifs critical for kinase activity are not present in TRR-1, TRRAP, or Tra1p (Hunter et al., *Cell* 83: 1-4, 1995). Instead of having an enzymatic function, this domain of
30 TRRAP has been proposed to mediate protein-protein interactions (McMahon

et al., *Cell* 94: 363-74, 1998). All six *trr-1* mutations introduce nonsense codons (Figure 7B). *trr-1(n3637)* is predicted to truncate the protein just prior to the ATM/PI-3 kinase-like domain. The phenotypic strength of *trr-1(n3637)* is similar to that of other alleles, suggesting that deletion of the ATM/PI-3
 5 kinase-like domain alone results in a severe loss of protein function. Finally, *trr-1(n3630)*, *trr-1(n3637)*, and *trr-1(n3712)* introduce amber stop codons, and we observed that the sterility associated with these alleles was reduced by the *sup-5(e1464)* informational suppressor tRNA mutation. This suppression, along with the partially penetrant sterility caused by *trr-1(RNAi)*, confirms that
 10 the sterility observed in *trr-1* mutants is truly due to loss of *trr-1* function.

***trr-1(RNAi)* is synthetically lethal with mutations in *lin-35* Rb and other class B synMuv genes**

trr-1(RNAi) caused more severe phenotypic consequences than did *trr-1*
 15 mutations. For example, the ectopic induction phenotype of *lin-15A*; *trr-1(RNAi)* mutants was much stronger than that of *trr-1*; *lin-15A* mutant strains (Table 5). We do not believe this difference is reflective of a partial loss of gene function caused by all of the *trr-1* mutations. Instead we propose that at least some of the mutations cause a severe loss of gene function and that the
 20 difference is due to an effect of *trr-1(RNAi)* on maternally-provided gene activity. In support of this proposal, *trr-1(n3704)/mnDf87*; *lin-15A* and *trr-1(n3712)/mnDf87*; *lin-15A* mutants that were severely deficient in zygotically-provided *trr-1* activity but retained maternally-provided *trr-1* activity had phenotypic penetrances that were similar to those of *trr-1*; *lin-15A*
 25 homozygotes and were weaker than those of *lin-15A*; *trr-1(RNAi)* mutants. Also arguing that *trr-1*; *lin-15A* homozygotes have significantly reduced zygotically-provided *trr-1* gene activity, the protein truncations predicted by *trr-1(n3704)* and other *trr-1* mutations are likely to remove functional domains and compromise TRR-1 activity.

We further characterized the effects of *trr-1(RNAi)*. In wild-type and class A synMuv genetic backgrounds, *trr-1(RNAi)* caused retarded growth, adult sterility and weakly penetrant embryonic and larval lethalties (Table 6).

Table 6 *trr-1(RNAi)* is synthetically lethal with class B but not with class A synMuv mutations

Genotype	% dead embryos	% dead L1 larvae	Total % lethality
			(n)
wild-type	0	0	0 (1062)
<i>trr-1(RNAi)</i>	6.6	1.2	7.8 (726)
<i>lin-15A(n767)</i>	0	0	0 (823)
<i>lin-38(n751)</i>	0.1	0	0.1 (1003)
<i>lin-15B(n744)</i>	0.2	0	0.2 (1002)
<i>lin-35(n745)</i>	0.6	0.2	0.8 (482)
<i>lin-36(n766)</i>	0.3	0	0.3 (890)
<i>dpl-1(n2994)</i>	14	1.1	15.1 (265)
<i>lin-15A(n767); trr-1(RNAi)</i>	3.2	0.9	4.1 (470)
<i>lin-38(n751); trr-1(RNAi)</i>	3.8	1.3	5.1 (628)
<i>lin-15B(n744); trr-1(RNAi)</i>	62.5	36.0	98.5 (469)
<i>lin-35(n745); trr-1(RNAi)</i>	66.2	33.8	100 (263)
<i>lin-36(n766); trr-1(RNAi)</i>	19.4	21.6	41.0 (444)
<i>dpl-1(n2994); trr-1(RNAi)</i>	45.1	53.6	98.7 (304)

Animals injected with *trr-1* dsRNA were individually plated 10-15

- 5 hours following injection. Injected animals were subsequently transferred to new plates every 24 hours until egg laying had ceased. Dead embryos and larvae on a plate were counted at least two days after eggs were laid. All of the mutant strains in which *trr-1(RNAi)* was performed are homozygous viable.

- 10 Interestingly, *trr-1(RNAi)* caused highly penetrant embryonic and larval lethalties in combination with many class B synMuv mutations. Most of the dead embryos arrested at the late embryonic pretzel stage and those that

hatched died shortly thereafter. We have not yet determined a basis for this lethality. It is important to note that many of the class B synMuv mutations tested are predicted to have severe effects on their cognate class B synMuv proteins. Since *trr-1(RNAi)* can synthetically interact with strong reduction-of-
5 function or null class B synMuv mutations, these data indicate that *trr-1* functions redundantly with class B synMuv genes not only in vulval cell-fate determination but also in an essential process earlier in development.

trr-1(RNAi) causes synthetic lethality in a *lin-36(n766)* background although the penetrance of this lethality is not as high as in other class B
10 synMuv backgrounds. This assay therefore unmasks a redundancy between *trr-1* and *lin-36* that we did not observe in the P8.p induction assay. As discussed above, the strength of the *lin-36* defect may not be equivalent to the strengths of defects of other class B synMuv genes. This difference in strengths may explain why, relative to other class B synMuv genes, *lin-36*
15 shows weaker interactions with *trr-1* in terms of synthetic lethality and synthetic P8.p induction.

***trr-1* synthetically interacts with *dpl-1* DP**

Mammalian TRRAP and yeast Tra1p are thought to function as
20 coactivator proteins that bridge transcription factors to histone acetyltransferases (McMahon et al., *Cell* 94: 363-74, 1998; Brown et al., *Science* 292, 2333-7, 2001). Based on coimmunoprecipitation and functional assays, E2F transcription factors were linked to TRRAP (McMahon et al., *Cell* 94: 363-74, 1998; Lang et al., *J Biol Chem* 276: 32627-34, 2001). *In vivo* E2F
25 and DP family proteins form heterodimers that are bound by Rb family proteins via a direct interaction with the E2F subunit reviewed by (Dyson, *Genes Dev* 12: 2245-62, 1998; Trimarchi et al., *Nat Rev Mol Cell Biol* 3: 11-20, 2002). We previously determined that one of two *C. elegans* E2F family members, *efl-1*, and the sole DP family member, *dpl-1*, are class B synMuv genes Ceol et al., *Mol Cell* 7: 461-73 (2001). As noted above, *lin-35* Rb was also
30

characterized as a class B synMuv gene, and the LIN-35 Rb protein was found to form a complex with DPL-1 and EFL-1 *in vitro* (Lu et al., *Cell* 95: 981-91, 1998; Ceol et al., *Mol Cell* 7: 461-73, 2001).

LIN-35 Rb and Rb proteins in other species are thought to recruit histone
 5 deacetylase complexes to regulate E2F-dependent transcription
 (Brehm et al., *Nature* 391: 597-601, 1998; (Luo et al., *Cell* 92, 463-73, 1998; Magnaghi-Jaulin et al., *Nature* 391: 601-5, 1998). Coupling these results with our genetic finding that *trr-1* acts redundantly with *lin-35* Rb to negatively
 10 regulate vulval induction, one might speculate that EFL-1 and DPL-1 recruit distinct LIN-35-containing and TRR-1-containing complexes to appropriately regulate vulval cell fate determination. To examine this possibility, we wished to determine if *trr-1* acted through *efl-1* and *dpl-1* to negatively regulate vulval development.

Without being tied to a particular theory, three lines of evidence suggest
 15 that *trr-1* does not act solely through transcription factors, *efl-1* and *dpl-1*; first, the ectopic induction of P8.p in *dpl-1 trr-1* double mutants is greater than that observed in either single mutant (Figure 6). Because of the sterility conferred by the *dpl-1*(*n3316*) null and *trr-1*(*n3712*) mutations, these mutants were derived from *dpl-1*(*n3316*) *trr-1*(*n3712*) / ++ mothers. It is notable that in this
 20 test we substantially reduced maternally-provided *dpl-1* activity by injecting mothers with *dpl-1* dsRNA and scoring *dpl-1*(*n3316 RNAi*) *trr-1*(*n3712*) progeny; second, in a weak *lin-15A* mutant background at 15°C, *trr-1*(*RNAi*) greatly enhanced the ectopic induction observed in *dpl-1* mutant animals that were derived from *dpl-1* heterozygous mutant mothers (Table 7);

25

Table 7 *trr-1* acts redundantly with *dpl-1*

Genotype	Ave. # P(3-8).p induced	
	(±SE)	% animals mutant (n)
<i>lin-15A</i> (<i>n433</i>); <i>trr-1</i> (<i>RNAi</i>)	3.17 (±)	20 (15)
<i>dpl-1</i> (<i>n3316</i>); <i>lin-15A</i> (<i>n433</i>)	3.00 (±0)	0 (35)

*dpl-1(n3316); lin-15A(n433);*4.98 (\pm)

89 (45)

trr-1(RNAi)

Animals were raised at 15°C, a temperature at which *dpl-1(n3316); lin-15A(n433)* mutants do not show hyperinduction. *dpl-1(n3316)* homozygous mutants were recognized as the Unc non-Gfp progeny of *dpl-1(n3316) unc-4(e120)/ mIn1[dpy-10(e128) mIs14]* heterozygous parents.

5 third, when performed in a homozygous *dpl-1* mutant background, *trr-1(RNAi)* caused synthetic lethality with *dpl-1* (Table 6). Since viable *trr-1(RNAi) dpl-1* progeny could be derived from heterozygous, but not homozygous *dpl-1* mutant mothers, this synthetic lethality apparently required a lack of maternally-provided *dpl-1* activity. These results indicate that *trr-1* does not
 10 act only through *dpl-1* to regulate vulval development and embryonic and larval viability. Although all of these assays were conducted in *dpl-1* mutant backgrounds, we expect that, since reduction of *dpl-1* function is predicted to affect all *C. elegans* DP/E2F activity, these results similarly apply to *efl-1*.

In addition to these data, one other observation argues against the model
 15 that *trr-1* acts solely through *dpl-1*. Whereas double mutants containing *lin-35(n745)*, a putative null allele of *lin-35*, and *trr-1(n3712)* display highly penetrant ectopic induction of P8.p, the ectopic induction in *dpl-1(n3316 RNAi)* mutants is relatively weak (Figure 6). If both *lin-35* and *trr-1* were acting solely through *dpl-1*, defects of equivalent strengths would be expected.

20

The Muv phenotype of *trr-1* mutants requires *let-60* Ras pathway activity

Previous studies determined that a conserved Ras pathway induces vulval development in *C. elegans* reviewed by (Sternberg et al., *Trends Genet* 14: 466-72, 1998). Loss-of-function mutations affecting genes in this pathway
 25 cause a vulvaless (Vul) phenotype characterized by P(3-8).p adopting hypodermal instead of vulval cell fates. To determine if Ras pathway activity is required for the *trr-1* mutant phenotype, we constructed strains in which the functions of *trr-1*, *lin-15A* and a Ras pathway gene were reduced. The uninduced phenotype caused by *let-23* receptor tyrosine kinase and *let-60* Ras

mutations was epistatic to the hyperinduced phenotype caused by *trr-1* and *lin-15A* loss of function (Table 8).

Table 8 *trr-1* epistasis with *let-23* RTK, *let-60* Ras and *lin-3* EGF

Genotype	Ave. # P(3-8).p induced (\pm SE)	% animals hyperinduced	n
wild-type	3.00 (\pm 0)	0	31
<i>lin-15A(n767)</i>	3.00 (\pm 0)	0	24
<i>lin-15A(n767); trr-1(RNAi)</i>	5.60 (\pm 0.08)	100	44
<i>let-23(sy97); lin-15A(n767)</i>	0.02 (\pm 0.02)	0	28
<i>let-23(sy97); lin-15A(n767); trr-1(RNAi)</i>	0.05 (\pm 0.03)	0	42
<i>let-60(n1876); lin-15A(n767)</i>	0 (\pm 0)	0	17
<i>let-60(n1876); lin-15A(n767); trr-1(RNAi)</i>	0 (\pm 0)	0	23
<i>lin-3(n378); lin-15A(n767)</i>	0.30 (\pm 0.07)	0	40
<i>lin-3(n378); lin-15A(n767); trr-1(RNAi)</i>	4.35 (\pm 0.20)	85	20

5 *let-23(sy97)* homozygous mutants were recognized as Rol Unc non-Gfp progeny of *rol-6(e187) let-23(sy97) unc-4(e120)/mIn1[dpy-10(e128) mIs14]; lin-15A(n767)* heterozygous parents, and *let-60(n1876)* homozygous mutants were recognized as Unc progeny of *let-23(n1876) unc-22(e66)/nT1; +/nT1; lin-15A(n767)* heterozygous parents.

These results indicate that Ras pathway activity is required to produce the *trr-1; lin-15A* Muv phenotype. By contrast, *trr-1; lin-3; lin-15A* triple mutants showed a wild-type level of induction in P(5-7).p and ectopic induction in P3.p, P4.p and P8.p. *lin-3* encodes an EGF-like protein that is produced by the gonadal anchor cell and is thought to act non-cell autonomously to stimulate Ras pathway activity in P(5-7).p (Hill et al., *Nature* 358: 470-6, 1992).. These findings suggest that a basal level of *lin-3*-independent Ras pathway activity, when combined with mutations in *trr-1* and *lin-15A*, is sufficient to induce vulval cell fates in P(3-8).p.

hat-1 and *epc-1*, but not *ssl-1*, loss of function phenocopies *trr-1*

TRRAP and Tra1p are components of protein complexes that acetylate histones (Allard et al., *Embo J* 18: 5108-19, 1999; reviewed by Brown et al., *Trends Biochem Sci* 25:15-9, 2000). These complexes are distinguished by

their histone acetyltransferase subunits: the mammalian TFTC and p/CAF and the yeast SAGA complexes contain Gcn5 family acetyltransferases, whereas the mammalian TIP60 and the yeast NuA4 complexes contain MYST family acetyltransferases.

5 To determine if TRR-1 might function with a histone acetyltransferase in *C. elegans*, we used RNA-mediated interference to inactivate such genes. Whereas inactivation of a *Gcn5* homolog *Y47G6A.6* had no effect, inactivation of a MYST family gene we have named *hat-1* produced a highly penetrant Muv phenotype in a *lin-15A* background. To further characterize *hat-1*, we
10 isolated a deletion allele, *n4075*, that removes 1010 base pairs from the *hat-1* locus and is predicted to produce a protein that contains the first 35 amino acids of HAT-1 followed by 52 unrelated amino acids prior to termination (Figure 11A). The genomic nucleic acid sequence of *hat-1* is shown in Figure 12. The nucleic acid sequence of the *hat-1* open reading frame is shown in Figure 13.
15 The predicted full-length HAT-1 protein is 458 amino acids long, and this deletion is expected to remove the conserved chromodomain and acetyltransferase catalytic domain (Figure 11B). The amino acid sequence of the wild-type HAT-1 protein is shown in Figure 14. *hat-1(n4075)* mutants exhibited the same spectrum of phenotypes and genetic interactions as *trr-1*
20 mutants. *hat-1(n4075)* single mutants were slow growing and sterile. In combination with class A synMuv mutations, *hat-1(n4075)* caused a severe Muv phenotype characterized by P3.p, P4.p and P8.p ectopic induction (Table 8). Alone, *hat-1(n4075)* caused ectopic induction of P8.p (Figure 11C). In combination with a *lin-15B* mutation, the penetrance of this ectopic induction
25 was greatly increased (Figure 11D).

 The TIP60 and NuA4 complexes contain other proteins in addition to MYST family acetyltransferases. We inactivated *C. elegans* genes encoding homologs of these proteins and identified *epc-1* as a negative regulator of vulval induction. The genomic sequence of *epc-1* is shown in Figure 16. The
30 nucleic acid sequence of the *epc-1* open reading frame is shown in Figure 17.

epc-1 encodes a homolog of the *Drosophila* Enhancer of Polycomb (E(Pc)) protein and similarly named mammalian and yeast proteins. The deduced amino acid sequence of EPC-1 is shown in Figure 18. Aside from their association with MYST family histone acetyltransferases, little is known about the molecular interactions of E(Pc)-like proteins. Inactivation of *epc-1* caused fully penetrant embryonic lethality in the broods of animals injected with RNA. To study the effects of *epc-1* inactivation during postembryonic development, we injected *epc-1* RNA into RNAi-deficient hermaphrodites and subsequently mated these animals with RNAi-competent males, a procedure referred to as “zygotic RNAi” (Herman, *Development* 128: 581-90, 2001). For many genes that act during multiple stages of development, this scheme has been shown to provide sufficient gene activity for embryonic functions, but inadequate gene activity for postembryonic functions. *epc-1(RNAi)* performed in this manner did not affect vulval induction in wild-type animals, but produced a Muv phenotype in *lin-15A* and *lin-38* mutant backgrounds (Table 9).

Table 9 *hat-1* and *epc-1* but not *ssl-1* loss of function phenocopies *trr-1* loss of function

Genotype	Ave. # P(3-8).p	% animals	
	induced (\pm SE)	mutant	n
wild-type	3.00 (\pm 0)	0	31
<i>lin-15A(n767)</i>	3.00 (\pm 0)	0	24
<i>lin-38(n751)</i>	3.00 (\pm 0)	0	27
<i>lin-15B(n744)</i>	3.00 (\pm 0)	0	20
<i>hat-1(n4075)</i>	3.15 (\pm 0.08)	15	20
<i>hat-1(n4075); lin-15A(n767)</i>	3.76 (\pm 0.14)	76	25
<i>hat-1(n4075); lin-15B(n744)</i>	3.71 (\pm 0.10)	77	31
<i>rde-1/+; epc-1(RNAi)</i>	3.00 (\pm 0)	0	65
<i>rde-1/+; lin-15A(n767); epc-1(RNAi)</i>	3.32 (\pm 0.10)	36	33
<i>lin-38(n751); rde-1/+; epc-1(RNAi)</i>	3.29 (\pm 0.02)	31	65
<i>rde-1/+; lin-15B(n744); epc-1(RNAi)</i>	3.03 (\pm 0.02)	4.2	48

<i>rde-1/+; ssl-1(RNAi)</i>	3.00 (± 0)	0	37
<i>rde-1/+; lin-15A(n767); ssl-1(RNAi)</i>	3.00 (± 0)	0	42
<i>rde-1/+; lin-15B(n744); ssl-1(RNAi)</i>	3.01 (± 0.01)	2.9	70

hat-1(n4075) homozygous mutants were recognized as the non-Unc progeny of *+/nT1n754; hat-1(n4075)/nT1n754* heterozygous parents. Since RNAi of *epc-1* and *ssl-1* using standard methods causes highly penetrant embryonic lethality, we performed "zygotic RNAi" as described below.

- 5 A low percentage of P8.p induction was observed in a *lin-15B* background. We recently obtained a deletion allele that removes 886 bases from the *epc-1* locus, including the third and fourth *epc-1* exons (Figure 5A). If the second exon were spliced to the fifth exon, a 137 amino acid protein would be produced that contains the first 109 amino acids of the 795 amino acid
- 10 predicted EPC-1 protein. Preliminary studies indicate that *epc-1(n4076)* homozygotes are sterile and, with respect to vulval induction, show genetic interactions similar to those of *epc-1(RNAi)*, *trr-1* and *hat-1* mutants.

TRRAP copurified with the p400 protein as part of the mammalian TIP60 and p400 complexes (Fuchs et al., *Cell* 106: 297-307, 2001). The p400

15 complex was isolated based on its interaction with the adenovirus E1A oncoprotein and was also shown to associate with c-myc. The p400 protein itself is a member of the SWI2/SNF2 family of proteins, and, like many SWI2/SNF2 family members, was shown to possess ATPase activity. We identified a *C. elegans* homolog of p400, which we named *ssl-1* (*ssl*,

20 SWI2/SNF2-like). *ssl-1* genomic sequence and the predicted SSL-1 protein product are shown in Figure 19. Figure 16B shows the nucleotide positions of the predicted exons with respect to *ssl-1* genomic sequence. The cDNA sequence of *ssl-1* is shown in Figure 20. The deduced protein sequence is shown in Figure 21. The function of *ssl-1* was studied by RNAi. *ssl-1(RNAi)*

25 caused an embryonic lethal phenotype reminiscent of that caused by *epc-1(RNAi)*. In both cases, dead embryos generally arrested just prior to morphogenesis and apparently lacked the hypodermal ridge that is a characteristic of enclosed embryos. We are currently characterizing this phenotype further. "Zygotic" RNAi of *ssl-1*, using the same procedure as

described above, caused no vulval defects in wild-type, *lin-15A*, or *lin-15B* genetic backgrounds. These results suggest that *ssl-1* may act with *epc-1* in an essential embryonic process.

5 ***trr-1* acts redundantly with *lin-35* Rb to antagonize *let-60* Ras signaling**

Identifying factors involved in cell fate determination is important for understanding how cells that contain the same genomic information can adopt different cell fates during animal development. As they help to distinguish P3.p, P4.p and P8.p from P(5-7).p, *trr-1*, *hat-1*, and *epc-1* are such cell fate
10 determination genes. Given their molecular identities, *trr-1*, *hat-1*, and *epc-1* likely act at the level of transcription, either in an instructive or permissive fashion, to create differences in gene expression in P3.p, P4.p and P8.p as compared to P(5-7).p.

Many of the pathways involved in regulating cell fate determination are
15 conserved. In many cases, pathways that control cell fate determination in model organisms has been shown to regulate cellular proliferation in mammals. Pathways that regulate vulval cell fate specification in *C. elegans* provide clear examples. A conserved *let-60* Ras pathway induces vulval cell fates, and this pathway is antagonized by the class B *lin-35* Rb pathway. *trr-1*, and likely *hat-*
20 *1* and *epc-1*, act in parallel to *lin-35* Rb to negatively regulate *let-60* Ras pathway signaling. These comparisons suggest that mammalian counterparts of *trr-1*, *hat-1*, and *epc-1* may similarly act in parallel to Rb and antagonize Ras in the control of cell proliferation.

25 ***trr-1*, *hat-1*, and *epc-1* likely share a common function**

The vulval phenotypes and genetic interactions of *trr-1*, *hat-1*, and *epc-1* mutants are strikingly similar. In light of the copurification of their mammalian and yeast counterparts, these data strongly suggest that TRR-1, HAT-1, and EPC-1 proteins function as part of a protein complex. To
30 conclusively demonstrate such an interaction, strains containing mutations in

two of these genes will be constructed. If these mutants are acting in the same complex, one would not expect to observe synergism in double mutants. In addition, protein-protein interaction studies will be performed. This complex containing putative complex members, *trr-1*, *hat-1*, and *epc-1* were the only
5 candidates we identified by RNAi. It is possible that these three genes encode an indispensable core of a putative HAT complex that associates with other proteins whose functions are dispensable for proper vulval development. The large size of TRR-1 may require it to be divided into fragments to perform protein interaction studies.

10

***hat-1* mutants likely have defects in histone acetylation**

The best studied MYST family acetyltransferases are the yeast Esa1p and mammalian TIP60 proteins. Esa1p was found to preferentially acetylate histone H4 (Smith et al., *Proc Natl Acad Sci USA* 95: 3561-5, 1998; Clark et
15 al., *Mol Cell Biol* 19: 2515-26, 1999; Suka et al., *Mol Cell* 8: 476-9, 2001) Furthermore, depletion of Esa1p resulted in global reduction of the acetylation of H4 and, to a lesser extent, of other nucleosomal histones (Reid et al., *Mol Cell* 6, 1297-307, 2000; Suka et al., *Mol Cell* 8: 476-9, 2001). HAT-1 function is assayed using commercially available antisera that specifically recognize
20 acetylated isoforms of histones to determine whether *hat-1* mutants have gross defects in histone acetylation. Differences in acetylation between *hat-1* mutants and wild-type animals is determined by whole-mount staining of fixed animals or by chromatin immunoprecipitation.

25 Putative HAT complex function

Histone acetyltransferases have been characterized as transcriptional coactivators (reviewed by Roth et al., *Biochem* 70:81-120, 2001), and TRRAP and its yeast homolog Tra1p are proposed to bridge interactions between activation domains of DNA-binding transcription factors and histone
30 acetyltransferases (Brown et al., *Science* 292, 2333-7, 2001). Therefore, a

putative TRR-1/EPC-1/HAT-1 complex may function in transcriptional activation (Figure 22). If so, one would expect it to activate genes that negatively regulate vulval development.

While most data support the link between acetylation and activation, additional observations suggest that at least some histone acetylation may be important for gene silencing. For example, loss-of-function mutations that affect the MYST family acetyltransferases Sas2p and Sas3p cause defects in silencing of mating type loci and telomeres in yeast (Reifsnyder et al., *Nat Genet* 14:42-9, 1996; Ehrenhofer-Murray et al., *Genetics* 145:923-34, 1997). Sas2p and Sas3p are proposed to acetylate newly-deposited nucleosomes, and the modified acetyllysine residues they create are thought to be important for establishing silencing following DNA replication (Meijsing et al., *Genes Dev* 15: 3169-82, 2001; Osada et al. *Genes Dev* 15:3155-68, 2001). These residues may include acetyllysine 16 on histone H4, which is implicated in mating type loci and telomeric silencing in yeast (Johnson et al., *Embo J* 11: 2201-9, 1992; Meijsing et al., *Genes Dev* 15: 3169-82, 2001). Other acetylated histone isoforms are prevalent in silent chromatin. For instance, *Drosophila* heterochromatin is enriched in acetyllysine 12 of histone H4 (Turner et al., *Cell* 69: 375-84, 1992). Just as a MYST family histone acetyltransferase is linked to silencing, loss-of-function studies in *Drosophila* indicate a role for E(Pc) in transcriptional repression. *E(Pc)* mutations synergize with polycomb group mutations to strongly derepress homeobox genes and act alone as suppressors of variegation to derepress genes that are juxtaposed to heterochromatin (Sato et al., *Genetics* 105: 357-70, 1983; Sinclair et al., *Genetics* 148: 211-20, 1998). These observations allow us to consider the possibility that HAT-1, in association with TRR-1 and EPC-1, may normally downregulate transcription (Figure 22). By this model, one would expect a putative TRR-1/EPC-1/HAT-1 complex to silence genes that are required for vulval cell fates. Because we do not know the relevant targets of TRR-1/EPC-1/HAT-1, we cannot distinguish between transcriptional activating versus repressing models at this time.

Putative TRR-1/EPC-1/HAT-1 complex DNA targeting

Their coimmunoprecipitation and cooperation in reporter gene activation suggest that mammalian TRRAP can be targeted by E2F proteins to DNA (McMahon et al., *Cell* 94: 363-74, 1998; (Lang et al., *J Biol Chem* 276: 32627-34, 2001). We investigated the possibility of TRR-1 targeting by DP/E2F heterodimers by studying genetic interactions between *trr-1* and *dpl-1*. *dpl-1* is the only DP family member in *C. elegans* and therefore loss of *dpl-1* activity is expected to effectively reduce all DP/E2F heterodimer function in the organism. *dpl-1* synthetically interacted with *trr-1* in vulval induction and viability assays. It is especially relevant that we observed synergism in some of these assays when using *dpl-1(n3316 RNAi)* mutants, which are severely compromised for *dpl-1* function. These results combined with the observation that the defects of *trr-1* single mutants are stronger than those of *dpl-1* single mutants suggest that *trr-1* acts only partially or not at all through *dpl-1*. If not only through DPL-1, how might a putative TRR-1/EPC-1/HAT-1 complex be targeted to DNA? Studies in yeast indicate that the TRRAP homolog Tra1p directly interacts with acidic activation domains of transcription factors (Brown et al., *Trends Biochem Sci* 25: 15-9, 2000). TRR-1 may similarly be targeted to DNA by transcription factors other than DPL-1. The assays we have used to characterize *trr-1* provide a means of identifying and evaluating candidate transcription factors and other proteins that may function with TRRAP family members in targeted histone acetylation.

The experiments described in Example II were carried out as described below.

Strains and genetics

Strains were cultured as described by (Brenner, *Genetics* 77: 71-94, 1974), and maintained at 20°C unless otherwise specified. Bristol N2 was used as the wild-type strain. The following mutations were used: LGI: *lin-35(n745)*; LGII: *dpy-10(e128)*, *let-23(sy97)*, *rol-6(e187)*, *dpl-1(n2994, n3316)* (Chapters

2, 3), *unc-4(e120)*, *trr-1(n3630, n3637, n3704, n3708, n3709, n3712)* (This study), *mex-1(it9)*, *lin-38(n751)*; LGIII: *lon-1(e185)*, *sup-5(e1464)*, *lin-36(n766)*, *lin-37(n758)*; LGIV: *lin-3(n378)*, *let-60(n1876)* (Beitel et al., *Nature* 348: 503-9, 1990); LGV: *dpy-11(e224)*, *rde-1(ne219)*

5 (Tabara et al., *Cell* 99: 123-32, 1999); LGX: *lin-15B(n744)*, *lin-15A(n767, n433)* (Ferguson et al., *Genetics* 123: 109-21, 1989) and, unless otherwise noted, are described in (Riddle et al., *C. elegans II* (Cold Spring Harbor, New York, Cold Spring Harbor Laboratory Press, 1997). The deficiencies *mnDf90* and *mnDf87* (Sigurdson, et al., *Genetics* 108: 331-45, 1984), translocation *nT1*

10 *n754* (IV;V) (Ferguson et al., *Genetics* 110: 17-72, 1985), and chromosomal inversion *mIn1[dpy-10(e128) mIs14]* (Edgley et al., *Mol Genet Genomics* 266:385-95, 2001), were also used. *mIs14*, an integrated transgene linked to the chromosomal inversion *mIn1*, consists of a combination of GFP-expressing transgenes that allow *mIs14*-containing animals to be identified

15 beginning at the 4-cell stage of embryogenesis (Edgley et al., *Mol Genet Genomics* 266:385-95, 2001).

P(3-8).p induction assay

In the wild-type, P(5-7).p adopt vulval fates in which they divide during

20 the L3 larval stage to generate seven or eight descendants. P3.p, P4.p and P8.p adopt non-vulval fates, typically dividing once to generate two descendants that fuse with the hypodermis. Induction was scored in L4 hermaphrodites using Nomarski DIC microscopy by counting the number of descendants produced by individual P(3-8).p cells. Different scores, 1, 0.5 and 0 cells induced, were

25 assigned to cells that were fully, partially or not induced, respectively. Partially induced P(3-8).p cells have one daughter that produces a complement of induced descendants while the other daughter fails to divide.

***trr-1* cloning**

We mapped *trr-1* to an interval on LGII between the right endpoint of the deficiency *mnDf90* and the *mex-1* gene. To clone the *trr-1* gene, we performed transformation rescue as described by (Mello et al., *Embo J* 10: 3959-70, 1991), using the pRF4 plasmid (80 ng/μL) as a coinjection marker. We rescued the *trr-1* Muv and sterile phenotypes by injecting the cosmid C47D12 (10ng/μL) into *trr-1(n3712)/mIn1[dpy-10(e128) mIs14]; lin-15A(n767)* mutants and isolating Rol non-Gfp transgenic lines. *trr-1* corresponds to the predicted gene *C47D12.1*.

RNAi analyses

Templates for *in vitro* transcription reactions were made by PCR amplification of either cDNAs and their flanking T3 and T7 promoter sequences or coding exons from genomic DNA using T3 and T7-tagged oligonucleotides. *In vitro*-transcribed RNA was annealed and injected as described by (Fire et al., *Nature* 391: 806-11, 1998).

In addition to the genes described above, we injected RNA corresponding to *C. elegans* genes that encode homologs of the TRRAP complex proteins TIP48/TAP54α (*C. elegans* predicted gene *T22D1.1*), TIP49/TAP54 (C27H6.2), Eaf3p (Y37D8A.9), p33ING (Y51H1A.4), and AF-9 (M04B2.3) (Loewith et al., *Mol Cell Biol* 20: 3807-16, 2000; Eisen et al., *J Biol Chem* 276: 3484-91, 2001; Fuchs et al., *Cell* 106: 297-307, 2001; Nourani et al., *Mol Cell* 21: 7629-40, 2001; Gavin et al., *Nature* 415: 141-7, 2002; Ho et al., *Nature* 415: 180-3, 2002). We did not observe vulval lineage defects after injection of these RNAs into either wild-type or synMuv single mutant backgrounds.

Lastly, bacteria designed to express double-stranded RNA corresponding to the *Gcn5* homolog *Y47G6A.6* (Fraser et al., *Nature* 408: 325-30, 2000) were fed to wild-type and synMuv single mutant hermaphrodites. As described below, we did not observe vulval defects following this treatment.

Deletion allele isolation

Genomic DNA pools from mutagenized worms were screened for deletions essentially as described by (Plasterk et al., *Nat Genet* 17: 119-21, 1997). Deletion mutant animals were isolated from frozen stocks and were
5 backcrossed four times prior to use. *hat-1(n4075)* removes nucleotides +106 to +1115, *epc-1(n4076)* nucleotides +2014 to +2899 and *ssl-1(n4077)* nucleotides +5075 to +5757 of genomic DNA relative to their respective predicted translational start sites.

10 cDNA isolation

We used TITAN ONE-TUBE RT-PCR (Roche Diagnostics, Pleasanton, California) to carry out RT-PCR and recovered *trr-1* and *hat-1* cDNA clones. Existing cDNAs were obtained from the *C. elegans* EST project to determine gene structures of *epc-1*, the *trr-1* 3' end and the *ssl-1* 5' end. We used 5'
15 RACE (5' RACE System v2.0, GIBCO) to determine the 5' ends and SL1 *trans*-spliced leader sequences of *trr-1*, *hat-1*, and *epc-1* transcripts.

Allele sequence

We used PCR-amplified regions of genomic DNA as templates in
20 determining mutant allele sequences. For each allele investigated, we determined the sequences of all exons and splice junctions of the gene in question. All mutations were confirmed by determining the sequence of independently-derived PCR products. All sequences were determined using an automated ABI 373 DNA sequencer (Applied Biosystems).

25

Example III

ssl-1*, a p400 SWI/SNF ATPase homolog, acts redundantly with *lin-15B

TRRAP is a component of the mammalian p400 complex, which contains the p400 SWI/SNF family protein and was identified based on its
30 interaction with the adenovirus E1A oncoprotein (Fuchs et al., *Cell* 106: 297-

307, 2001). Although Tip60 was not present in the purified p400 complex, the Tip60 and p400 complexes share many of the same components and more recent analyses have indicated that p400 and Tip60 can copurify as part of a large p400/Tip60 multisubunit complex (Frank et al., EMBO Rep., 4:575-80, 5 2003).

As discussed in Example II, the *ssl-1* (*ssl*, SWI/SNF-like) gene encodes a homolog of the p400 protein. RNAi of *ssl-1* using standard methods caused fully penetrant embryonic lethality like that observed with *epc-1* (RNAi). zygotic RNAi of *ssl-1*, performed as described above, did not cause defects in 10 vulval development in either class A or class B synMuv backgrounds. In further studies, we isolated a deletion mutation, *n4077*, that removes a portion of the fifth *ssl-1* exon. *ssl-1*(*n4077*) is predicted to encode a truncated protein containing the first 540 amino acids of the 1671 amino acid SSL-1 protein and two unrelated amino acids. *ssl-1*(*n4077*) homozygotes were partially sterile 15 and produced a few inviable embryos, but were not defective in vulval development. *ssl-1*(*n4077*); *lin-15A*(*n767*) mutants were likewise not defective in vulval development, however, *ssl-1*(*n4077*); *lin-15B*(*n744*) mutants often expressed an ectopic vulval cell fate in P8.p. *ssl-1*(*n4077*) likely causes a stronger reduction in gene activity than does *ssl-1* zygotic RNAi, and this 20 stronger reduction unmasks a redundancy between *ssl-1* and *lin-15B*.

***trr-1*; *hat-1*, *trr-1*; *epc-1* and *trr-1*; *ssl-1* double mutants do not show synthetic defects in vulval development**

Whereas synthetic defects in double mutants imply genetic redundancy, 25 the lack of synthetic defects in double mutants can indicate that two genes act in the same genetic pathway. Based on the similar phenotype and genetic interactions of *trr-1*, *hat-1* and *epc-1* mutants and on the copurification of the proteins encoded by their mammalian and yeast counterparts, we hypothesized that *trr-1*, *hat-1* and *epc-1* act together to regulate vulval development. To test 30 this possibility, we constructed double mutants to determine if *hat-1* and *epc-1*

function redundantly with *trr-1*. We measured the numbers of vulval cell fates in *trr-1(n3712); hat-1(n3681)*, *trr-1(n3712); hat-1(n4075)*, and *trr-1(n3712); epc-1(RNAi)* mutants and found that the extent of vulval development observed in these double mutants was similar to that observed in single mutant animals.

- 5 These results suggest that *hat-1* and *epc-1* act in the same genetic pathway as *trr-1*, which by analogy to the class A and class B *lin-35* Rb synMuv pathways, we have named the class C synMuv pathway.

- trr-1; ssl-1* double mutants, and, as described above, *ssl-1; lin-15A* mutants were not synthetically defective in P(3-8).p cell-fate specification. It is
 10 possible that *ssl-1* has both class C and class A synMuv activities, however, additional considerations suggest that *ssl-1* has properties more like those of a class C gene. For instance, *ssl-1; synmuvB* mutants have a defect limited to P8.p, whereas *synmuvA; synmuvB* mutants typically show ectopic vulval cell fates in P3.p, P4.p and P8.p. In addition, *ssl-1* mutants are sterile, and sterility
 15 has not been observed for any class A synMuv gene (Thomas et al., *Development* 126: 3449-59, 1999). These considerations, along with the copurification of the mammalian SSL-1 and HAT-1 counterparts, p400 and Tip60, suggest that *ssl-1* is an atypical class C gene, one that acts redundantly with class B, but not class A synMuv genes.

20

***trr-1, hat-1, epc-1* and *ssl-1* act redundantly with the *lin-35* Rb pathway to antagonize *let-60* Ras signaling**

- Identifying genes involved in cell-fate determination is important for understanding how cells that contain the same genomic information can adopt
 25 different fates during animal development. As they help to distinguish P3.p, P4.p and P8.p from P(5-7).p, *trr-1, hat-1, epc-1* and *ssl-1* are such cell-fate determination genes.

- In many cases, pathways that control cell-fate determination and cell division in invertebrates have been shown to regulate similar processes in
 30 mammals. Pathways that regulate vulval cell-fate specification in *C. elegans*

provide clear examples. A conserved *let-60* Ras pathway induces vulval cell fates, and this pathway is antagonized by an at least partially conserved class B *lin-35* Rb pathway. *trr-1*, *hat-1*, *epc-1* and *ssl-1* act in parallel to *lin-35* Rb and other genes in this pathway to negatively regulate *let-60* Ras signaling. We

5 suggest that the mammalian counterparts of *trr-1*, *hat-1*, *epc-1* and *ssl-1* may similarly act in parallel to Rb and antagonize Ras in the control of cell-fate determination and cell division. It is interesting to note that the p400 complex and Rb-containing complexes are targeted by the adenovirus E1A oncoprotein (Whyte et al., Nature 334:124-9, 1988; Fuchs et al., Cell 106: 297-307, 2001).

10 Our finding regarding *ssl-1* redundancy with a *lin-35* Rb pathway gene suggests that E1A may act in mammals by perturbing the activities of functionally redundant p400 and Rb-containing complexes.

Identification of new class B synMuv genes

15 On the basis of genetic interactions, the synMuv genes have been grouped into three classes A, B and C. For an animal to show vulval abnormalities, genes representing two of three classes must be dysfunctional. The class B synMuv genes include genes that encode homologs of the mammalian Rb tumor suppressor protein and other proteins that act with Rb in

20 regulating cell-fate specification and division in mammals. We have recently discovered three new class B synMuv genes: *lin(n3628)*, *lin(n4256)*, and *lin-65*. *lin(n3628)* encodes a protein similar to the yeast Set2 histone methyltransferase. The nucleic acid and amino acid sequences of *lin(n3628)* are shown in Figures 23 and 24, respectively. *lin(n4256)* encodes a protein

25 similar to yeast and mammalian SUV39H1 family histone methyltransferases. The nucleic acid and amino acid sequences of *lin(n4256)* are provided in Figures 25 and 26. *lin-65* encodes a protein rich in acidic amino acids. The nucleic acid and amino acid sequences of *lin-65* are provided in Figures 27 and 28.

The striking parallel between the Rb pathway in mammals and the Rb-related pathway we have identified in worms suggests that further characterization of the synthetic Multivulva genes will provide insights into how cell proliferation is regulated in humans. Because synMuv genes encode members of a conserved tumor suppressor pathway that antagonizes a conserved Ras oncogene pathway, the class B synMuv genes are likely to be important in understanding cancer progression in mammals. Provided with the human genome sequence, standard methods can be used to identify mammalian orthologs of newly-identified synMuv genes. Such homologs may act as tumor suppressors or oncogenes in mammals. Genetic enhancer or suppressor screens may be performed to identify new genes which may function in or interface with this Rb-related pathway. Furthermore, using methods described herein, drug screens can be used to identify compounds that affect cell proliferation. Compounds that block the Muv phenotype of synMuv mutant animals are likely to be useful antitumor agents for the treatment of a mammalian neoplasia.

Compounds that stimulate cell division in animals with a single, silent synMuv mutation are likely to be agonists of cell proliferation and may act in a manner analogous to growth factors. Such compounds are useful in the treatment of a subject in need of increased cell proliferation, for example, in a subject that has a disorder characterized by increased cell death, such as Alzheimer's disease, Huntington's disease, stroke, Parkinson's disease, myocardial infarction or congestive heart failure.

Identifying synMuv targets [*Craig: please confirm that this paragraphs reflects our discussion of the screens***]**

The targets of synMuv biological activity, for example, genes that are transcriptionally regulated by a synMuv nucleic acid or polypeptide, are identified using a variety of genetic and molecular approaches. While target identification is discussed below for the class B synMuvs, similar approaches

are used to identify the targets of the class C synMuvs or other transcriptional regulatory systems.

At least two genetic screens can be used to identify class B synMuv targets. Both screens are based on the premise that the class B synMuv proteins negatively regulate transcription. Given that class B synMuv proteins are likely to negatively regulate transcription, one would postulate that the Muv phenotype of synMuv mutants is due to the ectopic expression of class B targets. Loss of function mutations in such targets likely suppress the synMuv phenotype. In one example, a simple F₂ suppression screen is used to identify such targets. In fact, such screens have identified Class B suppressor mutations that may affect such genes. Many of the isolates from these screens are as yet uncharacterized.

In a second example, which would likely identify genes whose expression is negatively regulated by the class B synMuvs, mutagenized class A synMuv F₁ animals are screened for a Muv phenotype. Dominant mutations expected from this screen might affect regulatory sequences bound by synMuv proteins and lead to ectopic expression of the target gene in question. Mutations of this type have been shown to affect the expression of *egl-1*, a gene that promotes programmed cell death in *C. elegans*. These *egl-1(gf)* mutations disrupt a binding site for the TRA-1 transcriptional repressor protein, leading to ectopic *egl-1* expression in the hermaphrodite specific neurons and subsequent programmed cell death (Conradt et al. *Cell* 98:317-27, 1999).

Because transcription factors typically target multiple genes, loss of function of one target may not suppress the phenotype caused by a transcriptional repressor loss of function or, alternatively, recapitulate the phenotype caused by transcriptional activator loss of function. Such challenges are overcome by performing screens in a particularly sensitized genetic background so as to allow the observation of a small effect that may be caused by loss of one target. For example, in one of the screens described above, the Muv phenotype caused by a temperature-sensitive *lin-15AB* allele was

suppressed. A similarly sensitized background may be used for to carry out F₂ suppression and F₁ synMuv screens.

Various molecular approaches involving microarrays are also useful in identifying synMuv targets. In the simplest experiment, expression profiles of synMuv mutants are compared to the wild type. A comparison of synMuv double mutant to the wild type can be problematic because these animals have different amounts of vulval tissue. The generation of vulval tissue likely involves the differential regulation of many genes, only a subset of which might be direct targets of synMuvs. Alternatively, a synMuv single mutant can be compared to a wild-type control. This approach may not succeed if two classes of synMuvs must lose function in order for transcription to be differentially regulated. If mutations in two classes of synMuvs are desired, an appropriate comparison may, for example, be that of a synMuvA; synMuvB; *let-60* Ras triple mutant versus a *let-60* Ras single mutant. These animals would fulfill the requirements of having the same amount of vulval tissue and disabling two classes of synMuvs. Alternatively, chromatin immunoprecipitation (ChIP) combined with microarray analysis may be used. For example, in a preparation of proteins crosslinked to DNA, DPL-1 or EFL-1 could be immunoprecipitated, the crosslink reversed and the resultant DNA amplified and applied to microarrays. Such microarray experiments described above may identify synMuv targets that could be compared to putative *let-60* Ras pathway targets as previously determined by microarray analyses (Romagnolo et al., Dev Biol 247:127-36, 2002). Determining this interface is clearly an important issue as Rb and Ras pathways antagonize each other not only in *C. elegans*, but also during cell cycle progression in cultured mammalian cells (Mittnacht et al., Curr Biol. 7:219-21, 1997; Peeper et al., Nature. 386:177-81, 1997).

Do the synMuv genes act by regulating cell cycle progression?

Many studies of Rb and E2F in mammals have focused on the roles of these proteins in cell cycle regulation. Might the class B synMuv genes, and possibly other classes of synMuv genes regulate vulval development through direct regulation of P(3-8).p cell cycles? While not being tied to a particular theory, the following observations support this possibility. For example, P3.p, P4.p, and P8.p undergo extra cell divisions in synMuv mutants. Additionally, mutations in a subset of class B synMuv genes that includes *dpl-1*, *efl-1*, and *lin-35* Rb have been shown to partially suppress the S phase and cell division defects caused by RNA-mediated interference of the *C. elegans* cyclin D homolog *cyd-1* (Boxem et al., Curr Biol. 12:906-11, 2002). There are other aspects of these observations that complicate a strict cell cycle regulation model. First, not only are there extra P3.p, P4.p and P8.p cell divisions in synMuv mutants, but there are also various changes in the differentiation of P3.p, P4.p and P8.p descendants in synMuv mutants. The synMuv genes therefore appear to regulate a cell fate decision, a component of which is the decision to progress through the cell cycle. Studies of Rb in mammals have indicated that Rb may have a role in halting cell cycle progression and stimulating differentiation during myogenesis (reviewed by Kitzmann Cell Mol Life Sci. 58:571-9, 2001). Second, whereas *dpl-1*, *efl-1*, and *lin-35* Rb mutations can partially suppress defects caused by *cyd-1(RNAi)*, mutations in other class B synMuv genes cannot (Boxem et al., Curr Biol. 12:906-11, 2002). This observation suggests that, if the class B synMuv genes are cell cycle regulators, some of them act in a tissue-specific fashion, for example in P(3-8).p but not in the intestinal cells that were monitored in *cyd-1(RNAi)* studies. Monitoring cell cycle progression in P3.p, P4.p and P8.p will address these issues.

The identification of synMuv transcriptional targets will enable us to identify their mammalian orthologs. Such targets are promising clinical targets for chemotherapeutics for the treatment of neoplasia. In addition, the

identification of synMuv protein-protein interactions is useful in screening for chemotherapeutic drugs that modulate such interactions.

Identification of Additional Mammalian Orthologs

Because the Rb and RAS pathways are conserved between mammals and *C. elegans*, the powerful genetics and genomics of *C. elegans* can be exploited, as described herein, for the systematic identification of mammalian genes that correspond to *C. elegans* genes identified according to methods described herein. Such genes include mammalian orthologs of synMuv class B, and class C genes and their transcriptional targets.

Protein sequences corresponding to genes of interest are retrieved from the repositories of *C. elegans* sequence information at the wormbase web site. The *C. elegans* protein or nucleic acid sequence is then used for standard [BLASTP] or [tblastn] searching using the NCBI website. The protein sequence corresponding to the top mammalian candidate produced by tblastn is retrieved from Genbank and is used for BLASTp search of *C. elegans* proteins using the wormbase website. These methods allow us to identify mammalian orthologs of worm genes revealed by our genetic analysis.

An ortholog is a protein that is functionally related to a reference sequence. Such orthologs might be expected to functionally substitute for one another. For example, expression of a mammalian ortholog of a *C. elegans* gene, when expressed in a worm having a mutation in the *C. elegans* gene, might be expected to partially or completely rescue the worm phenotype.

RNAi in mammalian cell lines

RNAi has been used extensively to deplete mRNAs in mammalian cell culture (Elbashir et al., Nature 411:494-8, 2001). Mammalian orthologs of class C synMuv genes can be identified using RNAi, for example, in mammalian cultured cells. Briefly, an inhibitory nucleic acid is introduced into a mammalian cell having a mutation in a class A or class B synMuv gene, for example, by lipofection. Such cells are then assayed for increased levels of cell

proliferation relative to control cells not contacted with an inhibitory nucleic acid. An increased level of proliferation in mammalian cells contacted with the inhibitory nucleic acid identifies the corresponding target gene as a class C synMuv gene.

5

Microarrays

The class B and class C genes described herein, are useful in identifying their transcriptional regulatory targets. Such targets may be identified using microarrays in combination with chromatin immunoprecipitation (chIP) as described herein. Such methods are described in U.S. Patent 6,503,717, 6,410,243, and 6,610,489, hereby incorporated by reference. A nucleic acid target of a class B or class C synMuv polypeptide will likely have a mammalian ortholog. Such an ortholog represents a promising target for the development of novel chemotherapeutics for the treatment of a neoplasia.

15 The array elements, which are preferably derived from the *C. elegans* genome, are organized in an ordered fashion such that each element is present at a specified location on the substrate. Useful substrate materials include membranes, composed of paper, nylon or other materials, filters, chips, glass slides, and other solid supports. The ordered arrangement of the array elements allows hybridization patterns and intensities to be interpreted as expression levels of particular genes or proteins. Methods for making nucleic acid microarrays are known to the skilled artisan and are described, for example, in U.S. Patent No. 5,837,832, Lockhart, et al. (Nat. Biotech. 14:1675-1680, 1996), and Schena, et al. (Proc. Natl. Acad. Sci. 93:10614-10619, 1996), herein incorporated by reference. Methods for making polypeptide microarrays are described, for example, by Ge (Nucleic Acids Res. 28:e3.i-e3.vii, 2000), MacBeath et al., (Science 289:1760-1763, 2000), Zhu et al. (Nature Genet. 26:283-289), and in U.S. Patent No. 6,436,665, hereby incorporated by reference.

30

Nucleic acid microarrays

To produce a nucleic acid microarray oligonucleotides may be synthesized or bound to the surface of a substrate using a chemical coupling procedure and an ink jet application apparatus, as described in PCT application
5 W095/251116 (Baldeschweiler et al.), incorporated herein by reference. Alternatively, a gridded array may be used to arrange and link cDNA fragments or oligonucleotides to the surface of a substrate using a vacuum system, thermal, UV, mechanical or chemical bonding procedure.

A nucleic acid molecule (e.g. RNA or DNA) derived from a biological
10 sample, such as a cultured cell, a tissue specimen, or other source, may be used to produce a hybridization probe as described herein. The mRNA is isolated according to standard methods, and cDNA is produced and used as a template to make complementary RNA suitable for hybridization using standard methods. The RNA is amplified in the presence of fluorescent nucleotides, and
15 the labeled probes are then incubated with the microarray to allow the probe sequence to hybridize to complementary oligonucleotides bound to the microarray.

Incubation conditions are adjusted such that hybridization occurs with precise complementary matches or with various degrees of less
20 complementarity depending on the degree of stringency employed. For example, stringent salt concentration will ordinarily be less than about 750 mM NaCl and 75 mM trisodium citrate, preferably less than about 500 mM NaCl and 50 mM trisodium citrate, and most preferably less than about 250 mM NaCl and 25 mM trisodium citrate. Low stringency hybridization can be
25 obtained in the absence of organic solvent, e.g., formamide, while high stringency hybridization can be obtained in the presence of at least about 35% formamide, and most preferably at least about 50% formamide. Stringent temperature conditions will ordinarily include temperatures of at least about 30°C, more preferably of at least about 37°C, and most preferably of at least
30 about 42°C. Varying additional parameters, such as hybridization time, the

concentration of detergent, e.g., sodium dodecyl sulfate (SDS), and the inclusion or exclusion of carrier DNA, are well known to those skilled in the art. Various levels of stringency are accomplished by combining these various conditions as needed. In a preferred embodiment, hybridization will occur at
5 30°C in 750 mM NaCl, 75 mM trisodium citrate, and 1% SDS. In a more preferred embodiment, hybridization will occur at 37°C in 500 mM NaCl, 50 mM trisodium citrate, 1% SDS, 35% formamide, and 100 µg/ml denatured salmon sperm DNA (ssDNA). In a most preferred embodiment, hybridization will occur at 42°C in 250 mM NaCl, 25 mM trisodium citrate, 1% SDS, 50%
10 formamide, and 200 µg/ml ssDNA. Useful variations on these conditions will be readily apparent to those skilled in the art.

The removal of nonhybridized probes may be accomplished, for example, by washing. The washing steps that follow hybridization can also vary in stringency. Wash stringency conditions can be defined by salt
15 concentration and by temperature. As above, wash stringency can be increased by decreasing salt concentration or by increasing temperature. For example, stringent salt concentration for the wash steps will preferably be less than about 30 mM NaCl and 3 mM trisodium citrate, and most preferably less than about 15 mM NaCl and 1.5 mM trisodium citrate. Stringent temperature conditions
20 for the wash steps will ordinarily include a temperature of at least about 25°C, more preferably of at least about 42°C, and most preferably of at least about 68°C. In a preferred embodiment, wash steps will occur at 25°C in 30 mM NaCl, 3 mM trisodium citrate, and 0.1% SDS. In a more preferred embodiment, wash steps will occur at 42°C in 15 mM NaCl, 1.5 mM trisodium
25 citrate, and 0.1% SDS. In a most preferred embodiment, wash steps will occur at 68°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. Additional variations on these conditions will be readily apparent to those skilled in the art.

A detection system may be used to measure the absence, presence, and
30 amount of hybridization for all of the distinct sequences simultaneously (e.g.,

Heller et al., Proc. Natl. Acad. Sci. 94:2150-2155, 1997). Preferably, a scanner is used to determine the levels and patterns of fluorescence.

Protein Microarrays

5 Families of proteins, such as those encoded by the genes described herein, or their orthologs, may be analyzed using protein microarrays. Such arrays are useful in high-throughput low-cost screens to identify peptide or candidate compounds that bind a polypeptide of the invention, or fragment thereof. Typically, protein microarrays feature a protein, or fragment thereof,
10 bound to a solid support. Suitable solid supports include membranes (e.g., membranes composed of nitrocellulose, paper, or other material), polymer-based films (e.g., polystyrene), beads, or glass slides. For some applications, proteins (e.g., polypeptides encoded by class B or class C synMuv gene or antibodies against such polypeptides) are spotted on a substrate using any
15 convenient method known to the skilled artisan (e.g., by hand or by inkjet printer). Preferably, such methods retain the biological activity or function of the protein bound to the substrate

The protein microarray is hybridized with a detectable probe. Such probes can be polypeptide, nucleic acid, or small molecules. For some
20 applications, polypeptide and nucleic acid probes are derived from a biological sample taken from a patient, such as a homogenized tissue sample (e.g. a tissue sample obtained by biopsy); or cultured cells (e.g., lymphocytes). Probes can also include antibodies, candidate peptides, nucleic acids, or small molecule compounds derived from a peptide, nucleic acid, or chemical library.
25 Hybridization conditions (e.g., temperature, pH, protein concentration, and ionic strength) are optimized to promote specific interactions. Such conditions are known to the skilled artisan and are described, for example, in Harlow, E. and Lane, D., Using Antibodies : A Laboratory Manual. 1998, New York: Cold Spring Harbor Laboratories. After removal of non-specific probes, specifically
30 bound probes are detected, for example, by fluorescence, enzyme activity (e.g.,

an enzyme-linked colorimetric assay), direct immunoassay, radiometric assay, or any other suitable detectable method known to the skilled artisan.

Screening Assays

5 As discussed above, *C. elegans* class B and class C synMuv genes and their encoded proteins function in chromatin remodeling and antagonize the RAS pathway. Given that mechanisms for controlling mammalian cell cycle regulation and *C. elegans* vulval development are highly conserved, *C. elegans* and components of the *C. elegans* synMuv pathway are useful in screening
10 methods for chemotherapeutics and for the identification of novel clinical targets.

 Compounds that modulate the function of a Class B, or Class C synMuv nucleic acid or of their encoded proteins are likely to be useful in treating neoplasias. Based on this discovery, screening assays may be carried out to
15 identify compounds that modulate the action of a polypeptide or the expression of a nucleic acid sequence of the invention. Such compounds are useful in treating a neoplasia. The method of screening may involve high-throughput techniques. In addition, these screening techniques may be carried out in cultured mammalian cells or in animals (e.g., nematodes).

20 Any number of methods are available for carrying out such screening assays. In one working example, candidate compounds are added at varying concentrations to the culture medium of cultured cells expressing one of the nucleic acid sequences described herein. Gene expression is then measured, for example, by standard Northern blot analysis (Ausubel et al., supra) or RT-
25 PCR, using any appropriate fragment prepared from the nucleic acid molecule as a hybridization probe. The level of gene expression in the presence of the candidate compound is compared to the level measured in a control culture medium lacking the candidate molecule. A compound that promotes a decrease in the expression of a nucleic acid sequence disclosed herein or a
30 functional equivalent is considered useful in the invention; such a molecule

may be used, for example, as a therapeutic to delay or ameliorate human diseases associated with neoplasia or inappropriate cell cycle regulation. Such cultured cells include nematode cells (for example, *C. elegans* cells), mammalian, or insect cells.

5 In another working example, the effect of candidate compounds may be measured at the level of polypeptide production using the same general approach and standard immunological techniques, such as Western blotting or immunoprecipitation with an antibody specific for a polypeptide of the invention. For example, immunoassays may be used to detect or monitor the
10 expression of at least one of the polypeptides of the invention in an organism. Polyclonal or monoclonal antibodies (produced by standard techniques) that are capable of binding to such a polypeptide may be used in any standard immunoassay format (e.g., ELISA, Western blot, or RIA assay) to measure the level of the polypeptide. A compound that promotes a decrease in the
15 expression of the polypeptide is considered particularly useful. Again, such a molecule may be used, for example, as a therapeutic to ameliorate neoplasia.

In one example, candidate compounds are screened for those that specifically bind to and antagonize a synMuv B or synMuv C polypeptide. Such an interaction can be readily assayed using any number of standard
20 binding techniques and functional assays (e.g., those described in Ausubel et al., supra). For example, a candidate compound may be tested *in vitro* for interaction and binding with a polypeptide of the invention and its ability to modulate the cell cycle or decrease cell proliferation may be assayed by any standard technique (e.g., a *C. elegans* synMuv assay).

25 In one particular working example, a candidate compound that binds to a polypeptide may be identified using a chromatography-based technique. For example, a recombinant polypeptide of the invention may be purified by standard techniques from cells engineered to express the polypeptide (e.g., those described above) and may be immobilized on a column. A solution of
30 candidate compounds is then passed through the column, and a compound

specific for the polypeptide is identified on the basis of its ability to bind to the polypeptide and be immobilized on the column. To isolate the compound, the column is washed to remove non-specifically bound molecules, and the compound of interest is then released from the column and collected.

- 5 Compounds isolated by this method (or any other appropriate method) may, if desired, be further purified (e.g., by high performance liquid chromatography). In addition, these candidate compounds may be tested for their ability to cause cell death using any assay known to the skilled artisan. Compounds isolated by this approach may also be used, for example, as therapeutics to delay or
- 10 ameliorate human diseases associated with neoplasia. Compounds that are identified as binding to polypeptides of the invention with an affinity constant less than or equal to 10 mM are considered particularly useful in the invention.

- Potential antagonists include organic molecules, peptides, peptide mimetics, polypeptides, nucleic acids, and antibodies that bind to a nucleic acid
- 15 sequence or polypeptide of the invention and thereby increase or decrease its activity. Potential antagonists also include small molecules that bind to and occupy the binding site of the polypeptide thereby preventing binding to cellular binding molecules, such that normal biological activity is prevented.

- Each of the DNA sequences provided herein may also be used in the
- 20 discovery and development of therapeutic lead compounds. The encoded protein, upon expression, can be used as a target for the screening of therapeutics for the treatment of neoplasia. Additionally, the DNA sequences encoding the amino terminal regions of the encoded protein or Shine-Delgarno or other translation facilitating sequences of the respective mRNA can be used
- 25 to construct antisense, dsRNAs, or siRNA sequences to control the expression of the coding sequence of interest. Such sequences may be isolated by standard techniques (Ausubel et al., *supra*). The antagonists of the invention may be employed, for instance, to delay or ameliorate human diseases associated with neoplasia.

Optionally, compounds identified in any of the above-described assays may be confirmed as useful in delaying or ameliorating human diseases associated with neoplasia or inappropriate cell cycle regulation in either standard tissue culture methods or animal models and, if successful, may be
5 used as therapeutics for the treatment of neoplasia.

Small molecules of the invention preferably have a molecular weight below 2,000 daltons, more preferably between 300 and 1,000 daltons, and most preferably between 400 and 700 daltons. It is preferred that these small molecules are organic molecules.

10

Test Compounds and Extracts

In general, compounds capable of delaying or ameliorating human diseases associated with neoplasia are identified from large libraries of both natural product or synthetic (or semi-synthetic) extracts or chemical libraries
15 according to methods known in the art. Those skilled in the field of drug discovery and development will understand that the precise source of test extracts or compounds is not critical to the screening procedure(s) of the invention. Compounds used in screens may include known compounds (for example, known therapeutics used for other diseases or disorders).
20 Alternatively, virtually any number of unknown chemical extracts or compounds can be screened using the methods described herein. Examples of such extracts or compounds include, but are not limited to, plant-, fungal-, prokaryotic- or animal-based extracts, fermentation broths, and synthetic compounds, as well as modification of existing compounds. Numerous
25 methods are also available for generating random or directed synthesis (e.g., semi-synthesis or total synthesis) of any number of chemical compounds, including, but not limited to, saccharide-, lipid-, peptide-, and nucleic acid-based compounds. Synthetic compound libraries are commercially available from Brandon Associates (Merrimack, NH) and Aldrich Chemical (Milwaukee,
30 WI). Alternatively, libraries of natural compounds in the form of bacterial,

5 fungal, plant, and animal extracts are commercially available from a number of sources, including Biotics (Sussex, UK), Xenova (Slough, UK), Harbor Branch Oceanographics Institute (Ft. Pierce, FL), and PharmaMar, U.S.A. (Cambridge, MA). In addition, natural and synthetically produced libraries are produced, if desired, according to methods known in the art, e.g., by standard extraction and fractionation methods. Furthermore, if desired, any library or compound is readily modified using standard chemical, physical, or biochemical methods.

10 In addition, those skilled in the art of drug discovery and development readily understand that methods for dereplication (e.g., taxonomic dereplication, biological dereplication, and chemical dereplication, or any combination thereof) or the elimination of replicates or repeats of materials already known to function in neoplasia should be employed whenever possible.

15 When a crude extract is found to decrease cell proliferation or to suppress a synMuv phenotype, further fractionation of the positive lead extract is necessary to isolate chemical constituents responsible for the observed effect. Thus, the goal of the extraction, fractionation, and purification process is the careful characterization and identification of a chemical entity within the crude extract that inhibits cell proliferation or suppresses a synMuv phenotype. Methods of fractionation and purification of such heterogenous extracts are known in the art. If desired, compounds shown to be useful agents to delay or ameliorate human diseases associated with neoplasia are chemically modified according to methods known in the art.

Pharmaceutical Therapeutics

25 The invention provides a simple means for identifying compositions (including nucleic acids, peptides, small molecule inhibitors, and mimetics) capable of acting as therapeutics for the treatment of a neoplastic disease. Accordingly, a chemical entity discovered to have medicinal value using the methods described herein is useful as a drug or as information for structural modification of existing compounds, e.g., by rational drug design. Such

30

methods are useful for screening compounds having an effect on a variety of diseases characterized by inappropriate cell cycle regulation.

For therapeutic uses, the compositions or agents identified using the methods disclosed herein may be administered systemically, for example, formulated in a pharmaceutically-acceptable buffer such as physiological saline. Preferable routes of administration include, for example, subcutaneous, intravenous, interperitoneally, intramuscular, or intradermal injections that provide continuous, sustained levels of the drug in the patient. Treatment of human patients or other animals will be carried out using a therapeutically effective amount of a neoplastic disease therapeutic in a physiologically-acceptable carrier. Suitable carriers and their formulation are described, for example, in Remington's Pharmaceutical Sciences by E.W. Martin. The amount of the therapeutic agent to be administered varies depending upon the manner of administration, the age and body weight of the patient, and with the clinical symptoms of the neoplastic disease. Generally, amounts will be in the range of those used for other agents used in the treatment of a neoplastic disease, although in certain instances lower amounts will be needed because of the increased specificity of the compound. A compound is administered at a dosage that controls the clinical or physiological symptoms of a neoplastic disease as determined by, for example, measuring tumor size, cell proliferation, or metastasis.

Formulation of Pharmaceutical Compositions

Administration of a compound may be by any suitable means that is effective for the treatment of a neoplastic disease. Generally, compounds are admixed with a suitable carrier substance, and are generally present in an amount of 1-95% by weight of the total weight of the composition. The composition may be provided in a dosage form that is suitable for oral, parenteral (e.g., intravenous, intramuscular, subcutaneous), rectal, transdermal, nasal, vaginal, inhalant, or ocular administration. Thus, the composition may

be in form of, e.g., tablets, capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, creams, plasters, drenches, delivery devices, suppositories, enemas, injectables, implants, sprays, or aerosols. The pharmaceutical compositions may be formulated according to conventional pharmaceutical practice (see, e.g., Remington: The Science and Practice of Pharmacy, (20th ed.) ed. A.R. Gennaro, 2000, Lippincott Williams & Wilkins, Philadelphia, PA. and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-2002, Marcel Dekker, New York).

10

Other Embodiments

From the foregoing description, it will be apparent that variations and modifications may be made to the invention described herein to adapt it to various usages and conditions. Such embodiments are also within the scope of the following claims.

15

All publications mentioned in this specification are herein incorporated by reference to the same extent as if each independent publication was specifically and individually indicated to be incorporated by reference.

20

What is claimed is:

Claims

1. A method for identifying a compound that treats a neoplasia, said method comprising the steps of:

5 (a) contacting a cell comprising a mutation in a Class B synMuv gene selected from the group consisting of: *mep-1*, *lin(n3628)*, *lin(n4256)*, and *lin-65* and a second mutation in a synthetic multivulval gene, or an ortholog thereof, with a candidate compound;

(b) detecting a phenotypic alteration in said contacted cell relative to a control cell; wherein a candidate compound that alters the phenotype of said
10 contacted cell relative to said control cell is a compound that treats a neoplasia.

2. The method of claim 1, wherein said cell is in a nematode.

3. The method of claim 2, wherein said phenotypic alteration is an
15 alteration in a multivulval phenotype.

4. The method of claim 2, wherein said phenotypic alteration is an alteration in sterility.

20 5. The method of claim 1, wherein said synthetic multivulval gene is a synMuv class A gene.

6. The method of claim 1, wherein said cell is an isolated mammalian cell.
25

7. The method of claim 1, wherein said phenotypic alteration is a decrease in cell proliferation.

8. A method for identifying a candidate compound that treats a neoplasia, said method comprising:

- (a) providing a cell having a mutation in a Class B synMuv gene selected from the group consisting of *mep-1*, *lin(n3628)*, *lin(n4256)*, and *lin-65*
5 and having a second mutation in a synMuv nucleic acid or ortholog thereof;
(b) contacting said cell with a candidate compound; and
(c) detecting a decrease in proliferation of said cell contacted with said candidate compound relative to a control cell not contacted with said candidate compound, wherein a decrease in proliferation identifies said candidate
10 compound as a candidate compound that treats a neoplasia.

9. The method of claim 8, wherein said cell is in a nematode.

10. The method of claim 9, wherein said decrease in proliferation is
15 detected by detecting inhibition of a Muv phenotype.

11. The method of claim 8, wherein said cell has a mutation in Dp, E2F, or histone deacetylase.

20 12. The method of claim 8, wherein said cell is an isolated mammalian cell.

13. A method of identifying a compound that treats a neoplasia, said method comprising:

(a) providing a cell expressing a nucleic acid having at least 95% identity to a Class B synMuv gene selected from the group consisting of: *mep-1*, *lin(n3628)*, *lin(n4256)*, and *lin-65*;

(b) contacting said cell with a candidate compound; and

(c) monitoring the expression of said nucleic acid, an alteration in the level of expression of said nucleic acid indicates that said candidate compound is a compound that treats a neoplasia.

10

14. The method of claim 13, wherein said gene comprises a reporter gene.

15. The method of claim 13, wherein said reporter gene comprises *lacZ*, *gfp*, CAT, or luciferase.

16. The method of claim 13, wherein said expression is monitored by assaying protein level.

17. The method of claim 13, wherein said expression is monitored by assaying nucleic acid level.

18. The method of claim 13, wherein said cell is in a nematode.

25

19. A method for identifying a candidate compound that treats a neoplasia, said method comprising:

(a) providing a cell expressing a Class B synMuv gene selected from the group consisting of: *mep-1*, *lin(n3628)*, *lin(n4256)*, and *lin-65*;

5 (b) contacting said cell with a candidate compound; and

(c) comparing the expression of said polypeptide in said cell contacted with said candidate compound to a control cell not contacted with said candidate compound, wherein an increase in the expression of said polypeptide identifies said candidate compound as a candidate compound that treats a
10 neoplasia..

20. The method of claim 19, wherein said cell is in a nematode.

21. The method of claim 19, wherein said expression is monitored
15 with an immunological assay.

22. A method for identifying a candidate compound that treats a neoplasia, said method comprising:

(a) providing a cell expressing a Class B synMuv polypeptide selected
20 from the group consisting of: MEP-1, LIN(n3628), LIN(n4256), and LIN-65, said method comprising;

(b) contacting said cell with a candidate compound; and

(c) comparing the biological activity of said polypeptide in said cell contacted with said candidate compound to a control cell not contacted with
25 said candidate compound, wherein an increase in the biological activity of said polypeptide identifies said candidate compound as a candidate compound that treats a neoplasia.

23. The method of claim 22, wherein said biological activity is
30 monitored with an enzymatic assay.

24. The method of claim 22, wherein said biological activity is monitored with an immunological assay.

5 25. The method of claim 22, wherein said biological activity is monitored with a nematode bioassay.

26. A method of identifying a nucleic acid target of class B synMuv biological activity, said method comprising:

- 10 (a) mutagenizing a *C. elegans* comprising mutations in a Class B synMuv gene selected from the group consisting of: *mep-1*, *lin(n3628)*, *lin(n4256)*, and *lin-65* and in a Class A synMuv gene;
- (b) allowing said *C. elegans* to reproduce; and
- (c) selecting a *C. elegans* comprising a mutation that suppresses a
- 15 synMuv phenotype; wherein said mutation identifies a nucleic acid target of class B synMuv biological activity.

27. A method of identifying a nucleic acid target of class B synMuv biological activity, said method comprising:

- 20 (a) providing a microarray comprising fragments of nematode nucleic acids;
- (b) contacting said microarray with detectably labeled nucleic acids derived from a nematode comprising a mutation in a Class B synMuv gene selected from the group consisting of: *mep-1*, *lin(n3628)*, *lin(n4256)*, and *lin-65*
- 25 gene;
- (c) detecting an alteration in the expression of at least one nucleic acid of a *C. elegans* comprising a mutation in said Class B synMuv gene relative to the expression of said nucleic acid in a control nematode, wherein an alteration in said expression identifies said nucleic acid as a nucleic acid target of class B
- 30 synMuv biological activity.

28. The method of claim 27, wherein said *C. elegans* further comprises a mutation in a second synMuv gene.

5 29. The method of claim 27, wherein said *C. elegans* further comprises a mutation in a gene that results in a Vulvaless (Vul) phenotype.

30. A method for identifying a nucleic acid that binds a synMuv class B polypeptide, said method comprising:

- 10 (a) providing nucleic acids derived from a nematode cell;
- (b) crosslinking said nucleic acids and their associated proteins to form a nucleic acid-protein complex;
- (c) contacting said nucleic acid-protein complex with an antibody against a polypeptide selected from the group consisting of MEP-1,
- 15 LIN(n3628), LIN(n4256), and LIN-65;
- (d) purifying said nucleic acid-protein complex using an immunological method; and
- (e) isolating said nucleic acid, wherein said isolated nucleic acid is a nucleic acid that binds a synMuv class B polypeptide.

20

31. The method of claim 30, further comprising the following steps:

- (f) detectably labeling the nucleic acid of step (e);
- (g) contacting a microarray comprising *C. elegans* nucleic acid fragments with said detectably labeled nucleic acid; and
- 25 (h) detecting binding of said detectably labeled nucleic acid, wherein said binding identifies said nucleic acid as a nucleic acid that binds a synMuv class B polypeptide.

32. A vector comprising a nucleic acid having at least 95% identity to a Class B synMuv gene selected from the group consisting of: *mep-1*, *lin(n3628)*, *lin(n4256)*, and *lin-65*.

5 33. The vector of claim 32, wherein said synMuv gene is *mep-1* (SEQ ID NO:2).

34. The nucleic acid of claim 33, wherein said synMuv gene comprises a mutation selected from the group consisting of *n3680*, *n3702*, and
10 *n3703*.

35. The vector of claim 32, wherein said synMuv gene is *lin(n3628)* (SEQ ID NO:24).

15 36. The vector of claim 32, wherein said synMuv gene is *lin(n4256)* (SEQ ID NO:26).

37. The vector of claim 36, wherein said synMuv gene is *lin-65* (SEQ ID NO:28).

20

38. An isolated cell comprising the vector of claim 32.

39. A nematode comprising the nucleic acid of claim 32.

25 40. A nematode comprising a mutation in a Class B synMuv gene selected from the group consisting of: *mep-1*, *lin(n3628)*, *lin(n4256)*, and *lin-65*.

41. The nematode of claim 40, wherein said mutation is a *mep-1*
30 mutation selected from the group consisting of *n3680*, *n3702*, and *n3703*.

42. A purified nucleic acid comprising a sequence that hybridizes under high stringency conditions to a Class B synMuv nucleic acid selected from the group consisting of: *mep-1*, *lin(n3628)*, *lin(n4256)*, and *lin-65*.

5

38. An antibody against a Class B synMuv polypeptide selected from the group consisting of: MEP-1, LIN(n3628), LIN(n4256), and LIN-65.

38. A method for identifying a compound that treats a condition
10 characterized by inappropriate cell death, said method comprising the steps of:

(a) contacting a nematode comprising a mutation in a Class B synMuv gene selected from the group consisting of: *mep-1*, *lin(n3628)*, *lin(n4256)*, and *lin-65* with a candidate compound;

(b) detecting a *muv* phenotype in said contacted nematode relative to a
15 control nematode; wherein a candidate compound that alters the phenotype of said contacted nematode relative to said control nematode is a compound that treats a condition characterized by inappropriate cell death.

39. The method of claim 38, wherein said cell is in a nematode.

20

40. The method of claim 38, wherein said alteration is an alteration in synMuv phenotype.

41. A method for identifying a compound that treats a neoplasia, said method comprising the steps of:

(a) contacting a cell comprising a mutation in a gene encoding KIAA1732 and a second mutation in a synMuv nucleic acid, or an ortholog thereof, with a candidate compound;

(b) detecting a phenotypic alteration in said contacted cell relative to a control cell; wherein a candidate compound that alters the phenotype of said contacted cell relative to said control cell is a compound that treats a neoplasia.

42. The method of claim 1, wherein said synthetic multivulval gene is a synMuv class A gene.

43. The method of claim 1, wherein said cell is an isolated mammalian cell.

44. The method of claim 1, wherein said phenotypic alteration is a decrease in cell proliferation.

45. A method for identifying a candidate compound that treats a neoplasia, said method comprising:

(a) providing a cell having a mutation in a nucleic acid encoding KIAA1732 and having a second mutation in a synMuv nucleic acid, or ortholog thereof;

(b) contacting said cell with a candidate compound; and

(c) detecting a decrease in proliferation of said cell contacted with said candidate compound relative to a control cell not contacted with said candidate compound, wherein a decrease in proliferation identifies said candidate compound as a candidate compound that treats a neoplasia.

46. The method of claim 8, wherein said cell has a mutation in Dp, E2F, or histone deacetylase.

47. The method of claim 5, wherein said cell is an isolated
5 mammalian cell.

48. A method of identifying a compound that treats a neoplasia, said method comprising:

- 10 (a) providing a cell expressing a nucleic acid having at least 95% identity to a nucleic acid that encodes KIAA1732; and
- (b) contacting said cell with a candidate compound; and
- (c) monitoring the expression of said nucleic acid, an alteration in the level of expression of said nucleic acid indicates that said candidate compound is a compound that treats a neoplasia.

15

49. The method of claim 8, wherein said gene comprises a reporter gene.

50. The method of claim 8, wherein said reporter gene comprises *lacZ*,
20 *gfp*, CAT, or luciferase.

51. The method of claim 8, wherein said expression is monitored by assaying protein level.

25 52. The method of claim 8, wherein said expression is monitored by assaying nucleic acid level.

53. The method of claim 12, wherein said cell is an isolated mammalian cell.

30

54. A method for identifying a candidate compound that treats a neoplasia, said method comprising:

- (a) providing a cell expressing a KIAA1732 polypeptide;
- (b) contacting said cell with a candidate compound; and
- 5 (c) comparing the expression of said polypeptide in said cell contacted with said candidate compound to a control cell not contacted with said candidate compound, wherein an increase in the expression of said polypeptide identifies said candidate compound as a candidate compound that treats a neoplasia.

10

55. The method of claim 54, wherein said cell is an isolated mammalian cell.

56. The method of claim 54, wherein said expression is monitored
15 with an immunological assay.

57. A method for identifying a candidate compound that treats a neoplasia, said method comprising:

- (a) providing a cell expressing a KIAA1732 polypeptide;
- 20 (b) contacting said cell with a candidate compound; and
- (c) comparing the biological activity of said polypeptide in said cell contacted with said candidate compound to a control cell not contacted with said candidate compound, wherein an increase in the biological activity of said polypeptide identifies said candidate compound as a candidate compound that
25 treats a neoplasia.

58. The method of claim 57, wherein said biological activity is monitored with an enzymatic assay.

59. The method of claim 57, wherein said biological activity is monitored with an immunological assay.

60. The method of claim 57, wherein said biological activity is
5 methyl transferase activity.

61. A method for identifying a nucleic acid that binds KIAA1732, said method comprising:

- (a) providing nucleic acids derived from a mammalian cell;
- 10 (b) crosslinking said nucleic acids and their associated proteins to form a nucleic acid-protein complex;
- (c) contacting said nucleic acid-protein complex with an anti-KIAA1732 antibody;
- (d) purifying said nucleic acid-protein complex using an immunological
15 method; and
- (e) isolating said nucleic acid, wherein said isolated nucleic acid is a nucleic acid that binds KIAA1732.

62. The method of claim 61, further comprising the following steps:
20 (f) detectably labeling the nucleic acid of step (e);
(g) contacting a microarray comprising human nucleic acid fragments with said detectably labeled nucleic acid; and
(h) detecting binding of said detectably labeled nucleic acid, wherein said binding identifies said nucleic acid as a nucleic acid that binds KIAA1732.

25

66. A vector comprising a nucleic acid having at least 95% identity to (SEQ ID NO:30).

67. An isolated cell comprising the vector of claim 26.
30

68. A method for identifying a compound that treats a neoplasia, said method comprising the steps of:

(a) contacting a nematode comprising a mutation in a Class C synMuv gene selected from the group consisting of *trr-1*, *hat-1*, *epc-1*, and *ssl-1* with a candidate compound; and

(b) detecting an altered phenotype in said contacted nematode relative to a control nematode; wherein a candidate compound that alters the phenotype of said contacted nematode relative to said control nematode is a compound that treats a neoplasia.

10

69. The method of claim 68, wherein said alteration is an alteration in vulval phenotype.

70. The method of claim 68, wherein said alteration is an alteration in sterility.

15

71. The method of claim 68, wherein said synMuv class C gene is *trr-1*.

72. The method of claim 71, wherein said mutations are selected from the group consisting of *n3630*, *n3637*, *n3704*, *n3708*, *n3709*, and *n3712*.

20

73. A method for identifying a candidate compound that treats a neoplasia, said method comprising:

(a) providing a cell having a mutation in a Class C synMuv gene selected from the group consisting of *trr-1*, *hat-1*, *epc-1*, and *ssl-1* nucleic acid and having a second mutation in a synMuv nucleic acid or ortholog thereof;

25

(b) contacting said cell with a candidate compound; and

(c) detecting a decreased proliferation of said cell contacted with said candidate compound relative to a control cell not contacted with said candidate

30

compound, wherein a decrease in proliferation identifies said candidate compound as a candidate compound that treats a neoplasia.

5 74. The method of claim 73, wherein said cell is in a nematode.

 75. The method of claim 73, wherein said nematode displays an alteration in a synMuv phenotype.

 76. The method of claim 73, wherein said cell comprises a mutation
10 in a class A or class B synMuv gene..

 77. A method for identifying a compound that treats a neoplasia, said method comprising the steps of:

 (a) contacting a nematode comprising a mutation in a Class C synMuv
15 gene selected from the group consisting of *trr-1*, *hat-1*, *epc-1*, and *ssl-1* and a second mutation in a Class A synthetic multivulval gene with a candidate compound;

 (b) detecting an altered phenotype in said contacted nematode relative to a control nematode; wherein a candidate compound that alters the phenotype
20 of said contacted nematode relative to said control nematode is a compound that treats a neoplasia.

 78. The method of claim 77, wherein said alteration is an alteration in synMuv phenotype.

25

 79. The method of claim 77, wherein said alteration is an alteration in sterility.

80. A method for identifying a compound that treats a neoplasia, said method comprising the steps of:

(a) contacting a nematode comprising a mutation in a Class C synMuv gene selected from the group consisting of *trr-1*, *hat-1*, *epc-1*, and *ssl-1* and a
5 second mutation in a Class B synthetic multivulval gene with a candidate compound;

(b) detecting an altered phenotype in said contacted nematode relative to a control nematode; wherein a candidate compound that alters the phenotype of said contacted nematode relative to said control nematode is a compound
10 that treats a neoplasia.

81. The method of claim 80, wherein said alteration is an alteration in synMuv phenotype.

15 82. The method of claim 80, wherein said alteration is an alteration in sterility.

83. A method for identifying a candidate compound that treats a neoplasia, said method comprising:

20 (a) providing a cell having a mutation in a Class C synMuv gene selected from the group consisting of *trr-1*, *hat-1*, *epc-1*, and *ssl-1* and having a second mutation in a synMuv gene or ortholog thereof;

(b) contacting said cell with a candidate compound; and

(c) detecting a decreased proliferation of said cell contacted with said
25 candidate compound relative to a control cell not contacted with said candidate compound, wherein a decrease in proliferation identifies said candidate compound as a candidate compound that treats a neoplasia.

84. The method of claim 83, wherein said cell is in a nematode.

30

85. The method of claim 83, wherein said nematode displays an alteration in a synMuv phenotype.

86. A method of identifying a compound that treats a neoplasia, said
5 method comprising:

(a) providing a cell expressing a nucleic acid having at least 95% identity to a Class C synMuv nucleic acid selected from the group consisting of *trr-1*, *hat-1*, *epc-1*, and *ssl-1*;

(b) contacting said cell with a candidate compound; and

10 (c) monitoring the expression of said nucleic acid, an alteration in the level of expression of said nucleic acid indicates that said candidate compound is a compound that treats a neoplasia.

87. The method of claim 86, wherein said gene comprises a reporter
15 gene.

88. The method of claim 86, wherein said reporter gene comprises *lacZ*, *gfp*, CAT, or luciferase.

20 89. The method of claim 86, wherein said expression is monitored by assaying protein level.

90. The method of claim 86, wherein said expression is monitored by assaying nucleic acid level.

25 91. The method of claim 86, wherein said nucleic acid is in a nematode.

92. A method for identifying a candidate compound that treats a neoplasia, said method comprising:

- (a) providing a cell expressing a a Class C synMuv polypeptide selected from the group consisting of TRR-1, HAT-1, EPC-1, and SSL-1 polypeptide;
- 5 (b) contacting said cell with a candidate compound; and
- (c) comparing the expression of said polypeptide in said cell contacted with said candidate compound to a control cell not contacted with said candidate compound, wherein an increase in the expression of said polypeptide identifies said candidate compound as a candidate compound that treats a
- 10 neoplasia.

93. The method of claim 92, wherein said cell is in a nematode.

94. The method of claim 92, wherein said expression is monitored

15 with an immunological assay.

95. A method for identifying a candidate compound that treats a neoplasia, said method comprising:

- (a) providing a cell expressing a Class C synMuv polypeptide selected
- 20 from the group consisting of TRR-1, HAT-1, EPC-1, and SSL-1;
- (b) contacting said cell with a candidate compound; and
- (c) comparing the biological activity of said polypeptide in said cell contacted with said candidate compound to a control cell not contacted with said candidate compound, wherein an increase in the biological activity of said
- 25 polypeptide identifies said candidate compound as a candidate compound that treats a neoplasia.

96. The method of claim 95, wherein said cell is in a nematode.

97. The method of claim 95, wherein said biological activity is monitored with an enzymatic assay.

98. The method of claim 95, wherein said biological activity is monitored with an immunological assay.

99. A method of identifying a nucleic acid target of a synMuv Class C polypeptide, said method comprising:

(a) mutagenizing a *C. elegans* comprising a first mutation in a Class C synMuv gene selected from the group consisting of *trr-1*, *hat-1*, *epc-1*, and *ssl-1* and a second mutation in a Class A or Class B synMuv gene;

(b) allowing said *C. elegans* to reproduce;

(c) selecting a *C. elegans* comprising a mutation that suppresses a synMuv phenotype; wherein said mutation identifies a nucleic acid target of a synMuv class C polypeptide.

100. The method of claim 99, wherein said second mutation is in a class A synMuv gene.

101. The method of claim 31, wherein said second mutation is in a Class B synMuv gene.

102. A method for identifying a nucleic acid target of a synMuv Class C polypeptide, said method comprising:

(a) providing a *C. elegans* comprising a mutations in a Class C synMuv gene selected from the group consisting of *trr-1*, *hat-1*, *epc-1*, and *ssl-1*;

(b) growing said *C. elegans* on bacteria expressing a dsRNA; and

(c) identifying a dsRNA that suppresses a synMuv phenotype; wherein said dsRNA identifies a nucleic acid target of a synMuv class C polypeptide.

103. A method for identifying a a nucleic acid target of a synMuv class C polypeptide, said method comprising:

(a) providing a *C. elegans* comprising mutations in a Class C synMuv gene selected from the group consisting of *trr-1*, *hat-1*, *epc-1*, and *ssl-1* and in
5 a Class A or Class B synMuv gene;

(b) growing said *C. elegans* on bacteria expressing a dsRNA; and

(c) identifying a dsRNA that suppresses a synMuv phenotype; wherein said dsRNA identifies a nucleic acid target of a synMuv class C polypeptide.

10 104. A method of identifying a nucleic acid whose expression is modulated by a synMuv class C polypeptide, said method comprising:

(a) providing a microarray comprising fragments of nematode nucleic acids;

(b) contacting said microarray with detectably labeled nucleic acids
15 derived from a nematode comprising a mutation in a Class C synMuv gene selected from the group consisting of *trr-1*, *hat-1*, *epc-1*, and *ssl-1* gene;

(c) detecting an alteration in the expression of at least one nucleic acid of a *C. elegans* comprising a mutation in said synMuv class C gene relative to the expression of said nucleic acid in a control nematode, wherein an alteration
20 in said expression identifies said nucleic acid as a nucleic acid modulated by a synMuv class C polypeptide.

105. The method of claim 104, wherein said *C. elegans* further comprises a mutation in a synMuv A or synMuv B gene.

25

106. The method of claim 104, wherein said *C. elegans* further comprises a mutation in a gene that results in a Vulvaless (Vul) phenotype.

107. The method of claim 104, wherein said gene encodes LET-60.

30

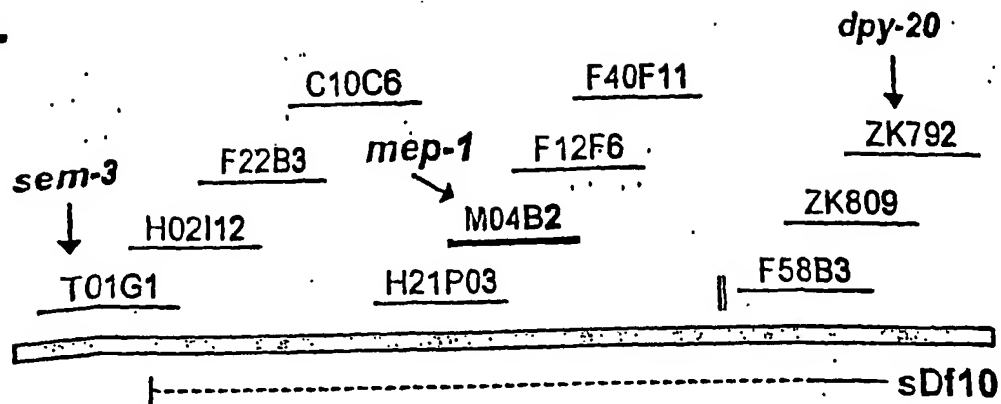
108. A method for identifying a nucleic acid target of a synMuv class C polypeptide, said method comprising:

- (a) providing nucleic acids derived from a nematode cell;
- (b) crosslinking said nucleic acids and their associated proteins to form a
5 nucleic acid-protein complex;
- (c) contacting said nucleic acid-protein complex with an antibody that binds a polypeptide selected from the group consisting of TRR-1, HAT-1, EPC-1, AND SSL-1;
- (d) purifying said nucleic acid-protein complex using an immunological
10 method; and
- (e) isolating said nucleic acid, wherein said isolated nucleic acid is a nucleic acid that binds a synMuv class C polypeptide.

109. The method of claim 108, further comprising the following steps:
- 15 (f) detectably labeling the nucleic acid of step (e);
 - (g) contacting said detectably labeled nucleic acid with a microarray comprising *C. elegans* nucleic acid fragments; and
 - (h) detecting binding of said detectably labeled nucleic acid, wherein said binding identifies said nucleic acid as a nucleic acid target of a synMuv
20 class C polypeptide.

FIGURE 1

A.



B.

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M V T A D E T V L A T T T N T T S M S V E P T D P R S A G E 30
S S S D S E P D T I E Q L K A E Q R E V M A D A A N G S E V 60
N G N Q E N G K E E A A S A D V E V I E I D D T E E S T D P 90
S P D G S D E N G D A A S T S V P I E E E A R K K D E G A S 120
E V T V A S S E I E Q D D D G D V M E I T E E P N G K S E D 150
T A N G T V T E E V L D E E E P E P S V N G T T E I A T E K 180
E P E D S S M P V E Q N G K G V K R P V E C I E L D D D D D 210
D E I Q E I S T P A P A K K A K I D D V K A T S V P E E D N 240
N E Q A Q K R L L D K L E E Y V K E Q K D Q P S S K S R K V 270
L D T L L G A I N A Q V Q K E P L S V R K L I L D K V L V L 300
P N T I S F P P S Q V C D L L I E H D P E M P L T K V I N R 330
M F G E E R P K L S D S E K R E R A Q L K Q H N P V P N M T 360
K L L V D I G Q D L V Q E A T Y C D I V H A K N L P E V P K 390
N L E T Y K Q V A A Q L K P V W E T L K R K N E P Y K L K M 420
H R Q G A V G G F Q L T E S K L V M S S Q H K E F N L Q H F T G S K F 450
Q G H M G K E T E P D T S E E D R M K D H E Y S E T M H L V I A K S E 480
E K E S K Y P C A I C E E D F N F K G V R E Q H Y K Q C K K 510
D Y I R I R N I M M P K Q D D H L Y I N R W L W E R P Q L D 540
P S I L Q Q Q Q Q A A L Q Q A Q Q K K Q Q Q L L H Q Q Q A A 570
Q A A A A A Q L L R K Q Q L Q Q Q Q Q Q Q Q A R L R E Q Q Q 600
A A Q F R Q V A Q L L Q Q Q S A Q A Q R A Q Q N Q G N V N H 630
N T L I A A M Q A S L R R G G Q Q G N S L A V S Q L L Q K Q 660
M A A L K S Q Q G A Q Q L Q A A V N S M R S Q N S Q K T P T 690
H R T P T F V Q E H T G C D A S S V G E E K E K Y L Q G H Q E G F A T H K 720
Q M V G K V L Q D M S G G A P L A K S H G R D E F F A V A G E E G 750
D E E R H L E V M S E H G L V T A D L L L K A Q K K E D G G R I C K 780
E T G C K N I A A G F E N M A G H H E V A A D D H Q V K L C S A E I M Y S 810
G D V A G A F E K G C S S Y G E T L E P A P H U T S E N H P K G D K K T S 840
T P A K K D D C I T L D D 853

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FIGURE 2

mep-1 genomic sequence:

TCACACACTCATGACATACACACATCATTTGCGCTCACACACCGCGCCGTGCG
CCATCCGACACCGCCCGGGTGGGACGTGTTCAAACCTTTTCGGTTTTCGTAAT
TAATAGTGAGCCCCGGTTTATTGCTTTGAGAATCAGTATAATGGATATATG
AGATTGTGTAATTAGGTTGCGTGCTTGAACCTTTAAAATTAACGTGTTTTAAAT
TTATCTGCCTTTATCGTTACAGTAAATCATTTTGATGAACCTTTTCGGATGAAT
CATAATGAAGTACGCGAGCGCTCTAACAAAATGTGTTTGTAATTCGAATTGC
TACAAGTTGCCCCGGCTTATTTTTTGGTGATTGAAGCATGATTCTGTTGACGC
TCCCGACGCGGAATACCAGGACGGACCGATGAGAGAGTACTGCCAGTGAA
GAGACGCATGCGAGCAGGACGAGTGCTGCTCACCTTCTTCTCAGCGTCG
GCGGCTGCGACCAGCGGCCGAGGAAGGGGAGGAGAGAGGCCGATTTGGC
TGCGTACCACGTTTGATACTCAGTCACTTACCACAGCTGGTTCTCTTGTCG
TTCAAATCTGGCTTGCCGCGCGCGCGCATTATTTCTACCAGTTTGAATCT
CCCACCTCTCCGACTGTAACGTCTCCTAATTTGCTTCCTTCTCATCACTCTCTC
TTTGCTTATTTCTCACTATCTAGACTCTATTTTTCCAGATGTCACCGCCGA
CGAGACGGTACTCGCCACAACGACCAACACCACTTCCATGTCTGTGGAACC
AACGGATCCGAGAAGCGCTGGTGAATCGTCCTCAGATTCGGAGCCAGACA
CAATTGAGGTGAGGAAAAGTTTTGGGAATTTAAATCTGAATAAAACGTTTTCA
GCAGCTGAAGGCAGAACAGCGCGAAGTGATGGCCGACGCGGCGAATGGTT
CCGAAGTCAACGGAAATCAAGAGAACGGAAAAGAGGAAGCGGCATCTGCA
GACGTGGAAGTGATCGAGATAGATGACACCGAAGAGTCTACGGATCCCTCA
CCTGATGGATCTGATGAAAACGGTGATGCTGCATCTACATCGGTTCCAATC
GAAGAGGAAGCGCGTAAAAAGGATGAGGGGGCTTCCGAAGTGAAGTGTGGC
ATCATCTGAGATTGAACAAGACGATGATGGCGATGTTATGGAAATCACTGAG
GAGCCGAACGGAAAGTCCGAGGATACTGCCAACGGAACAGGTGTGTTTTAT
AATTTTACCAAGTTTAATTTTAACTTTCTATTTTCAGTTACTGAGGAGGTGCTA
GATGAAGAGGAGCCAGAACCTTCCGTAAACGGAACTGAGATCGCTACA
GAGAAAGAGCCAGAAGATTCTTCAATGCCTGTGGAACAGAATGGGAAGGGT
GTGAAGCGGCCTGTGGAATGCATCGAACTCGACGACGACGATGATGACGA
GATTCAGGAAATTTCTACCCCTGCCCCAGCTAAAAAGCTAAAATTGATGAT
GTCAAGGCGACAAGCGTTCCAGAAGAGGACAACAATGAGCAGGCGCAGAA
GAGATTGCTCGACAAGCTGGAAGAGTATGTGAAGGAGCAGAAGGATCAACC
ATCCAGCAAAAGCCGAAAAGTTCTGGACACTCTTCTCGGAGCAATCAATGC
GCAAGTTCAAAGGAGCCTCTGTGCGTTCCGGAAGCTGATCCTGGACAAAGT
TCTCGTTCTCCCAACACAATATCATTCCCACCAAGTCAAGTTTGCGACTTAT
TGATTGAGCACGATCCCGAAATGCCTTTGACGAAGGTTATCAACAGGATGTT
TGGAGAAGAAAGACCAAGTTGAGTGATTCCGAGAAACGAGAGAGAGCTCA
GCTGAAACAACATAATCCTGTTCCAAATATGACAAAACCTGCTCGTGGACATT
GGACAGGATCTCGTTCAAGAAGCTACCTATTGTGATATAGTTACGCGGAAGA
ATCTTCCAGAGGTGCCAAAAAATCTTGAAACCTATAAGCAAGTCGCTGCGCA
GTTGAAACCAGTTTGGGAGACATTGAAACGCAAAATGAGCGGTACAAGTT
GAAAATGCATCGATGCGACGTCTGTGGATTCCAGACGGAATCAAAGCTGGT
TATGAGCACTACAAGGAGAATTTGCACTTCACAGGATCCAAATTCCAGTGC
ACCATGTGTAAAGAGACGCGACACGAGTGAGCAAAGAATGAAGGATCACTAC
TTGTAAGTTTTTTTTTTTTCATCTTTCAATATTCATTTAATTACAGCGAAACTC
ATCTTGTTATTGCAAAATCGGAAGAGAAGGAGTCCAAGTATCCATGTGCAAT

FIGURE 2

CTGCGAAGAAGACTTCAATTTCAAAGGTGTCCGTGAGCAGCATTACAAGCA
GTGCAAGAAGGACTACATTTCGCATTGAAACATCATGATGCCGAAGCAAGA
CGATCATCTCTATATCAACAGATGGCTCTGGGAGAGGCCCAATTGGATCC
CAGCATTCTTCAACAGCAGCAACAAGCTGCTCTTCAGCAAGCTCAACAAAAG
AAGCAACAGCAACTTCTGCATCAACAGCAAGCAGCACAAAGCTGCAGCCGCT
GCGCAACTCTTACGGAAGCAACAATTACAACAGCAACAACAACAGCAACAG
GCTCGTCTTCGTGAGCAACAGCAAGCGGCCCAATTCCGGCAAGTGGCTCAA
CTGCTGCAACAACAATCAGCGCAGGCTCAACGTGCACAGCAGAATCAAGGA
AATGTGAATCATAACACTCTGATTGCAGGTAATAGCTAAACATATTTTAAATA
AGTATTTTGTATAATTATTTATATTTTCAGCAATGCAAGCGTCGTTGCGTAGAG
GTGGTCAACAAGGAAATTCGCTGGCAGTTTCTCAACTTCTCCAAAAGCAAAT
GGCAGCTTTGAAGTCGCAACAAGGAGCTCAACAACCTTCAGGCTGCGGTGAA
CTCCATGAGAAGCCAGAACAGTCAAAAGACGCCAACACACAGAAGTTTCGAA
ACTTGTTACTACGCCGTCTCATGCTACTGTTGGCTCTTCTTCAGCTCCCACG
TTTGTATGCGAAATTTGTGATGCGTCAGTGCAGGAAAAGGAGAAGTATCTAC
AGCATCTTCAGGTAATTTTAAAGAAACGTTTCTATTTCAATTTCAAACCGATT
ATTAAATATCTTAAACATCACATTTTCAGACTACTCATAAGCAGATGGTTGGA
AAAGTGCTGCAGGACATGTCGCAAGGAGCTCCACTGGCATGTTCTCGATGC
CGTGACAGATTCTGGACTTATGAAGGGTTGGAGCGGCACCTTGGTGATGTG
CATGGTCTCGTCACTGCTGATCTGCTCCTCAAAGCGCAAAAGAAGGAAGAC
GGAGGTCGATGCAAGACATGCGGCAAGAACTATGCGTTCAACATGCTTCAA
CACTTGGTAGCTGATCATCAAGTGAAGTTGTGCTCGGCTGAAATCATGTACT
CGTGCGATGTGTGCGCGTTCAAATGCTCGAGTTATCAGACTCTGGAAGCCC
ATCTCACTTCAAATCACCCAAAAGGAGATAAGAAGACATCAACACCAGCAAA
AAAAGATGATTGTATTACTCTGGATGATTAAATAGGAAAACGAATGGCTTATC
CCGTTCTACGAATGAGTGCTGGAAACATTCTTCACAATGATCTCAATTATTT
TCTTATTCTTTACATTCAATCATTTTAAATCACCAAGTTCTCCCACTTTCAATTGA
TATACACATTCTATTGCGGGTTCCGGAACCGAAATCAATCAGTACTTTACTTT
ATTTCCCAATTTTTCTCTTCATGATATCTGGTTTATTCTCGCATCTTCCCCTA
CCTTCAAAACTCCCTATTTTTTTTTTCAAACCTAACTACCCACAAATTATCATG
TAAATCAAATTGCAATTCCTCATAAGACAGATCAGTATACACTTTCATTCA
TACGTCTGTTGTTCTCCCCATCTCATACTTTTTTTACCATTGTCCAGTTAA
GATTTTTGGAAGATATCTAT

FIGURE 3

mep-1 ORF

ATGGTCACCGCCGACGAGACGGTACTCGCCACAACGACCAACACCACTTCC
ATGTCTGTGGAACCAACGGATCCGAGAAGCGCTGGTGAATCGTCCTCAGAT
TCGGAGCCAGACACAATTGAGCAGCTGAAGGCAGAACAGCGCGGAAGTGAT
GGCCGACGCGGCGAATGGTTCCGAAGTCAACGGAAATCAAGAGAACGGAA
AAGAGGAAGCGGCATCTGCAGACGTGGAAGTGATCGAGATAGATGACACC
GAAGAGTCTACGGATCCCTCACCTGATGGATCTGATGAAAACGGTGATGCT
GCATCTACATCGGTTCCAATCGAAGAGGAAGCGCGTAAAAAGGATGAGGGG
GCTTCCGAAGTGAAGTGTGGCATCATCTGAGATTGAACAAGACGATGATGGC
GATGTTATGGAAATCACTGAGGAGCCGAACGGAAAGTCGGAGGATACTGCC
AACGGAACAGTTACTGAGGAGGTGCTAGATGAAGAGGAGCCAGAACCCTTCC
GTAAACGGAACAACCTGAGATCGCTACAGAGAAAGAGCCAGAAGATTCTTCA
ATGCCTGTCGAACAGAATGGGAAGGGTGTGAAGCGGCCTGTCGAATGCAT
CGAACTCGACGACGACGATGATGACGAGATTGAGGAAATTTCTACCCCTGC
CCCAGCTAAAAAAGCTAAAATTGATGATGTCAAGGCGACAAGCGTTCCAGA
AGAGGACAACAATGAGCAGGCGCAGAAGAGATTGCTCGACAAGCTGGAAG
AGTATGTGAAGGAGCAGAAGGATCAACCATCCAGCAAAAGCCGAAAAGTTC
TGGACACTCTTCTCGGAGCAATCAATGCGCAAGTTCAAAAGGAGCCTCTGT
CGGTTCCGAAGCTGATCCTGGACAAAGTTCTCGTTCTCCCAACACAATATC
ATTCCCACCAAGTCAAGTTTGCGACTTATTGATTGAGCACGATCCCGAAATG
CCTTTGACGAAGGTTATCAACAGGATGTTTGGAGAAGAAAGACCAAAAGTTGA
GTGATTCCGAGAAACGAGAGAGAGCTCAGCTGAAACAACATAATCCTGTTC
CAAATATGACAAAACCTGCTCGTGGACATTGGACAGGATCTCGTTCAAGAAG
CTACCTATTGTGATATAGTTCACGCGAAGAATCTTCCAGAGGTGCCAAAAAA
TCTTGAAACCTATAAGCAAGTCGCTGCGCAGTTGAAACCAGTTTGGGAGAC
ATTGAAACGCAAAAATGAGCCGTACAAGTTGAAAATGCATCGATGCGACGT
CTGTGGATTCCAGACCGGAATCAAAGCTGGTTATGAGCACTCACAAGGAGAA
TTTGCATTACAGGATCCAAATTCCAGTGCACCATGTGTAAAGAGACGGAC
ACGAGTGAGCAAAGAATGAAGGATCACTACTTCGAAACTCATCTTGTTATTG
CAAAATCGGAAGAGAAGGAGTCCAAGTATCCATGTGCAATCTGCGAAGAAG
ACTTCAATTTCAAAGGTGTCCGTGAGCAGCATTACAAGCAGTGCAAGAAGG
ACTACATTCGCATTGAAACATCATGATGCCGAAGCAAGACGATCATCTCTA
TATCAACAGATGGCTCTGGGAGAGGGCCCAATTGGATCCCAGCATTCTTCA
ACAGCAGCAACAAGCTGCTCTTCAGCAAGCTCAACAAAAGAAGCAACAGCA
ACTTCTGCATCAACAGCAAGCAGCACAAAGCTGCAGCCGCTGCGCAACTCTT
ACGGAAGCAACAATTACAACAGCAACAACAACAGCAACAGGCTCGTCTTCG
TGAGCAACAGCAAGCGGCCCAATTCCGGCAAGTGGCTCAACTGCTGCAACA
ACAATCAGCGCAGGCTCAACGTGCACAGCAGAATCAAGGAAATGTGAATCA
TAACACTCTGATTGCAGCAATGCAAGCGTCTGTTGCGTAGAGGTGGTCAACA
AGGAAATTCGCTGGCAGTTTCTCAACTTCTCCAAAAGCAAATGGCAGCTTTG
AAGTCGCAACAAGGAGCTCAACAACCTTCAGGCTGCGGTGAAGTCCATGAGA
AGCCAGAACAGTCAAAGACGCCAACACACAGAACTCCCACGTTTGTATGC
GAAATTTGTGATGCGTCAGTGCAGGAAAAGGAGAAGTATCTACAGCATCTTC
AGACTACTCATAAGCAGATGGTTGGAAAAGTGCTGCAGGACATGTGCGCAAG
GAGCTCCACTGGCATGTTCTCGATGCCGTGACAGATTCTGGACTTATGAAG
GGTTGGAGCGGCACTTGGTGATGTCGCATGGTCTCGTCACTGCTGATCTGC

FIGURE 3

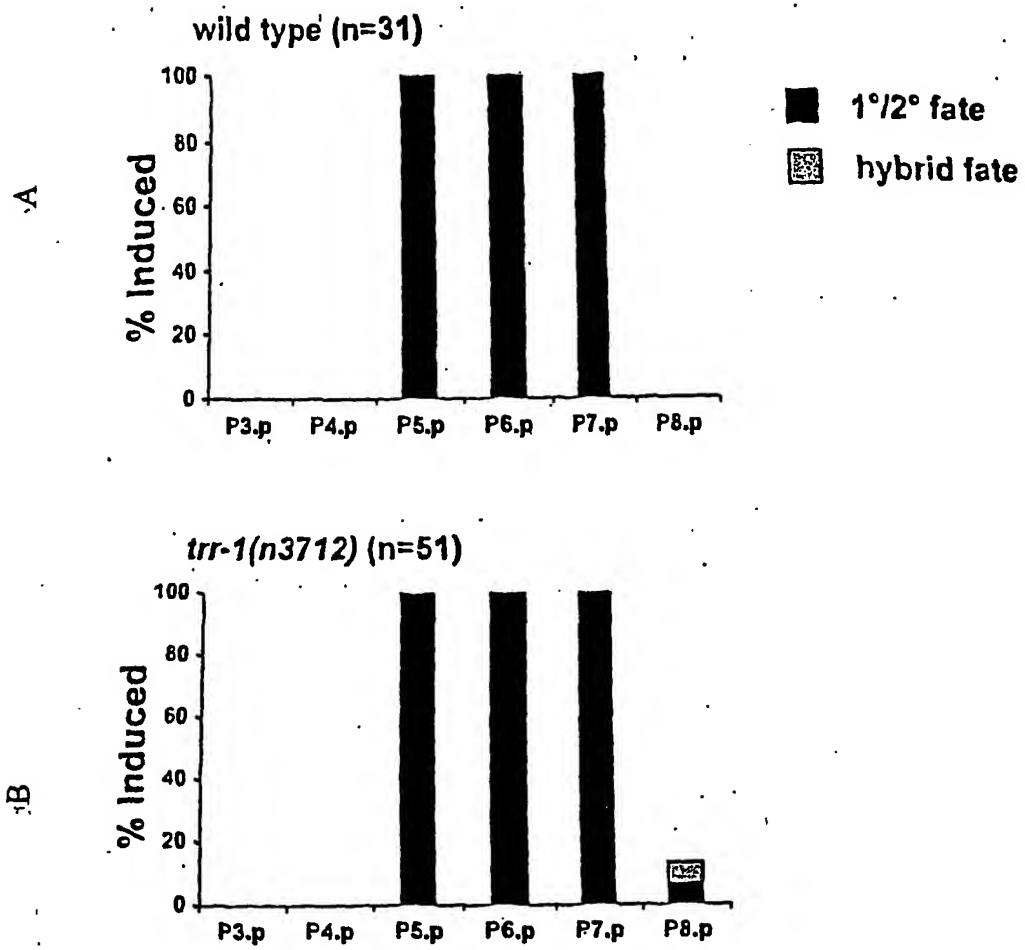
TCCTCAAAGCGCAAAAGAAGGAAGACGGAGGTCGATGCAAGACATGCGGC
AAGAACTATGCGTTCAACATGCTTCAACACTTGGTAGCTGATCATCAAGTGA
AGTTGTGCTCGGCTGAAATCATGTACTCGTGCGATGTGTGCGCGTTCAAAT
GCTCGAGTTATCAGACTCTGGAAGCCCATCTCACTTCAAATCACCCAAAAGG
AGATAAGAAGACATCAACACCAGCAAAAAAAGATGATTGTATTACTCTGGAT
GATTAA

FIGURE 4

MEP-1 protein

MYTADETVLATTTNTTSMŠVEPTDPRSAGESSSDSEPDTIEQLKAEQREVMAD
AANGSEVNGNQENGKEEAASADVEVIEIDDEESTDPSPDGSDENGDAASTSV
PIEEEARKKDEGASEVTVASSEIEQDDDGDMVEITEEPNGKSEDTANGTVTEEV
LDEEEPEPSVNGTTEIATEKEPEDSSMPVEQNGKGVKRPVECIELDDDDDDDEIQ
EISTPAPAKKAKIDDVKATSVPEEDNNEQAQKRLLDKLEEVKEQKDQPSSKSR
KVLDTLLGAINAQVQKEPLSVRKLILDKVLVLPNTISFPSPQVCDLLIEHDPEMPL
TKVINRMFGEERPRLSDSEKRERAQLKQHNPPVPMNTKLLVDIGQDLVQEATYC
DIVHAKNLPEVPKNLETYKQVAAQLKPWWETLKRKNPEPYKLKMHRCDVCGFQT
ESKLVMSTHKENLHFTGSKFQCTMCKETDTSEQRMKDHYFETHLVIKSEEKE
SKYPCAICEEDFNFKGVREQHYKQCKKDYIRIRNIMMPKQDDHLYINRWLWER
PQLDPSILQOQQQQAALQQAQKKQOQLLHQQQAAQAAAAAQLLRKQQLQQQ
QOQQQARLREQQQAQFRQVAQLLQOQSAQAQRAQQNQGNVNHNTLIAAM
QASLRGGQOQGNLAVSOLLQKQMAALKSOQGAQQLQAAVNSMRSQNSQKT
PTHRTPTFVCEICDASVQEKEKYLQHLQTTTHKQMVGVLDMSQGAPLACSR
CRDRFWTYEGLERHLVMSHGLVTADLLLKAQKKEDGGRCKTCGKNYAFNMLQ
HLVADHQVKLCSAEIMYSCDVCAFKCSSYQTLEAHLTSNHPKGDKKTSTPAKK
DDCITLDD

FIGURE 5



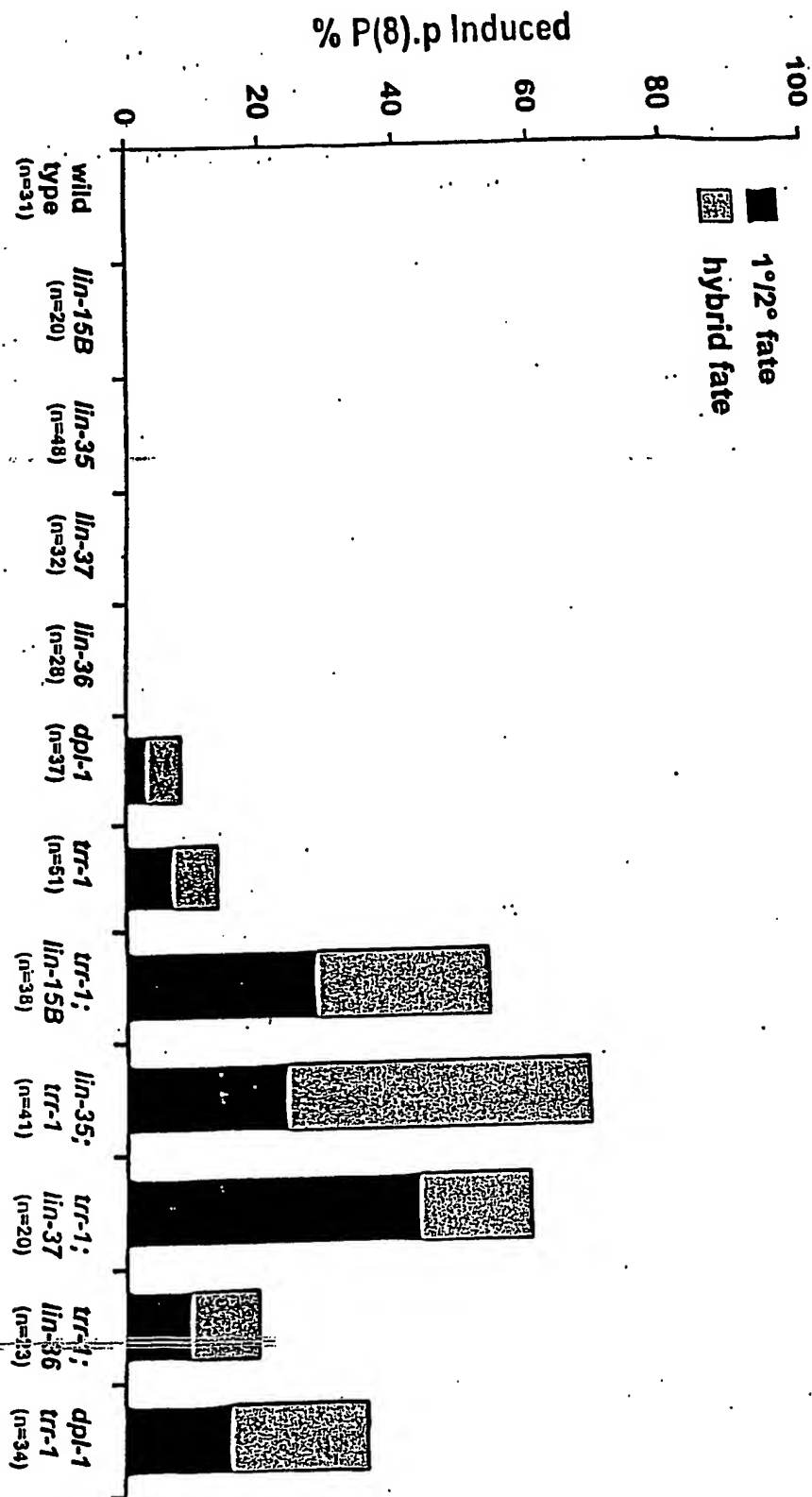
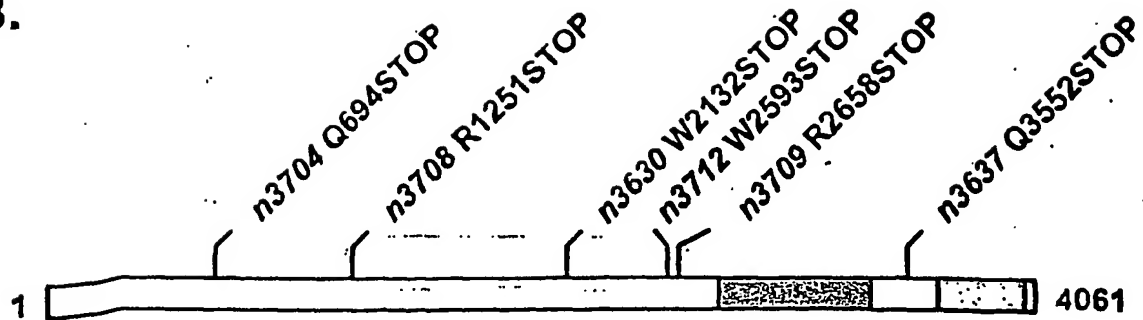
8/92
FIGURE 6

FIGURE 7

A.



B.



■ FAT domain (FRAP, ATM, TRRAP-like).
□ ATM/PI-3 kinase-like

10/92

FIGURE 8

lrr-1 genomic sequence:

GAGGAA GATGTAGACGACGATTCGGTTTCCGTACTCTCATGACTTTTGGCG
AAAATCCTCACGAATTCCTTTTCCGTCATACGTTGAGTTAAAAATCTGGCGAT
GTAACG AAGAATGAGAAGAGCGTTTGATGTTGCCATAAGTAGATTTTACTG
AAATAAGAAAAAGCTTTAATTAATATAATGATGATTTTTTTTCCAACCTCACT
TTTCGCATTGTTCTGATGTTTTAGTTCTGTGGCTCTGCGAAGGAAAAGTCG
AATAAATGCAGCGAAATTCCTGTTGTTTGTGTATTGTACATTAGACATTGAA
GATGATCATCTAAAGCAGATTCCAAAGCGATTCCGGGTGTCTCTAAACGATTA
TAACATTTTTAAAGCTTTTGCCTAATTTAATCCTTACTCGTCGTCATCATCAA
ACTTGAGACTGAAAGAGAGAAGTTTGTTCCAAAATGGGTCAATAATCGTCGAC
AGGTTCCAAACCGCTGAGTTTCTTCAGATAAATAATCTCCTGTAAGACCGTT
TCCTTGGTTATAACTGATCCCATGTGTCTGAAATTTGTTATTACACTGTTAAT
AATCATAAAAATAAAAGAAAAAGTCAAGAAAGGGTCAAATATTAATCAGGTCA
CATCTTTTTTATTCAATAAATCTCCTCTCTCGTTCGTGGCAATGCACGTGAA
ATGCGCCAACAACCGCGAGTGCGCCAACACACACACATACGCGTCAGCAG
ACAATTCGCTCTCGTTTGAAATTTAGTTGTTTCTTTGTTTCTGCTGAAATAAT
GTCAGTTTTCCGATAATTCAGCGTTTTCTGACTGATTTTTCTTGTTGCATT
ACTTCCTAATAGTTCATTCTACTCCATTCTTCATTTTATAATCTGTTTCCTTCG
CAATTTAGTGAATTAACACGTAAATCTTGTTTCAGATAAATTATTCAAATAGT
TGCACAAAGCTCAATAGTTTAGAAGTATCTTCAGTGCTGGTCACTAATAACAA
AATG GATCCGGCTATGGCTTCTCCAGGCTATCGGTCTGTGCAGTCCGATCG
GAGTAATCACCTAACAGAGCTGGAAACGAGAATTCAAATCTTGCCGATAAT
TCACAAAGAGATGATGTCAAATTGAAAATGTTACAAGTTAGTTTCAATAATTC
GTGTTAAGTAATCAATTTGTTCCGGTTGCAGGAGATTTGGAGCACAAATCGAAA
ATCATTTCACACTAAGTTCGCACGAGAAAGTCGTGGAGAGGGCTCATTCTCTC
GTTCTTACAAGTTTTCTGCAACACAAGTCCACAGTTCATTGCTGAAAACAAT
ACACAACAGCTTCGAAAGTTAATGCTTGAAATCATTCTTCGACTTTCGAACG
TAGAAGCCATGAAACATCATAGCAAAGAAATTATCAAGCAGATGATGAGGCT
AATCACCGTGGAATGAGGAGAATGCCAATTTGGCTATCAAATTTGTCACC
GATCAAGGGAGAAGTACCGGCAAAATGCAATATTGCGGAGAGGTTTCACAG
ATAATGGTCTCCTTCAAACAATGGTCATTGATCTGACGGCGAGTGGTCTGA
GCTGGTGATATGTTCAACATAAAAGAGCATAAAGCTCCACCGTCAACTAGCT
CCGACGAGCAAGTCATCACTGAATATTTGAAGACTTGCTACTATCAACAAAC
GGTTCTTCTCAACGGAACGGAAGGAAAACCGCCATTAAAATACAATATGATT
CCATCAGCTCATCAGTCAACGAAGGTGCTCCTGGAGGTTCCGTATCTCGTG
ATTTTCTTCTATCAACATTTCAAACAGCGATCCAAACCGAAGCGCTTGATTT
CATGAGGCTTGGTCTTGATTTCTAAATGTGAGAGTTCCAGACGAGGATAAA
CTCAAAACAAATCAAATAATAACCGATGATTTTGTGAGTGCACAGTCCCGAT
TCCTGTCAATTCGTCAACATTATGGCTAAGATTCAGCGGTAAAGTTTCGTTTTT
TCAAGTTTTTTCTGTAATCCGATTTTTATTTTTAGTTTTATGGATCTTATCA
TGCAAAATGGACCGCTTCTAGTGTGCGGAACAATGCAGATGCTCGAGCGGT
GCCCCGGCTGATCTGATAAGTGTCCGACGAGAAGTTCTGATGGCTTTGAAGT
ATTTACATCTGGAGAAATGAAGTCGAAATCTTTCCAATGCTACCTCGACT
CATCGCTGAGGAGGTTGTTCTGGGAACAGGATTCACTGCGATTGAGCATTT
GCGAGTTTTCATGTATCAAATGCTAGCAGATCTGTTGCATCACATGCGAAAT
TCTATAGACTATGAAATGATCACACAGTAAGTTTGAATAAGACTTTCTGATGA

FIGURE 8

AAAATGTTGAAATTT CAGCGTGATTTTCGTATTCTGTCGCACTCTTCACGATC
CTAACAACCTCTTCTCAAGTCCAGATTATGTCTGCTCGGCTGCTCAACTCACT
GGCCGAATCTCTGTGCAAAATGATTCAATGATACCGTAAGACTTATTCTA
TCAATAATCGTATCTCACTTCGAAATAAGTTTCAGACTCGTGATCTGCTCATT
GAAATCCTGGAGTCGCACGTGGCCAAGCTCAAACTCTTGCAGTCTATCAC
ATGCCATTCTCTTCCAACAATACGGAACCGAAATAGACTACGAATACAAAA
GTTATGAGAGAGACGCCGAGAAACCTGGAATGAATATCCCAAAGGACACTA
TACGAGGAGTACCGAAACGAAGAATCCGTGCGGCTCTCCATTGATTGAGTTG
AAGAGCTGGAATTCCTGGCATCAGAACCATCCACGTGCGAAGATGCAGATG
AGAGTGGTGGAGATCCGAACAAGCTTCCTCCGCCAACAAAAGAGGGAAAGA
AAACGTCTCCCGAAGCGATTTTAACCGCCATGTCAACGATGACACCTCCTC
CATTGGCAATTGTTGAAGCTCGAAATCTTGTGAAGTATATAATGCATACGTG
TAAATTCTGACAGGACAATTGAGAATCGCCCGGCCATCACAGGATATGTAT
CATTGTTGGAAGGAGCGAGATTTATTGCAACGTCTTCTACGATATGGTGTA
TGTGTATGGATGTATTCTGTGCTTCCAACAACCTCGAAATCAACCACAAATGCA
TTCTTCAATGCGGACAAAAGATGAGAAAGATGCTCTGGAGTCGTTGGCAAA
CGTTTTTACAACAATCGACCATGCGATATTCCGGGAAATCTTCAAAAAGTAT
ATGGATTTCTTGATTGAAAGAATTTACAATCGGAACCTATCCATTGCAATTGAT
GGTGAACACCTTCTTGTTGCGAAATGAAGTGCCATTCTTCGCATCTACGATG
CTTTCATTCTTGATGTCTCGAATGAAATTGCTGGAAGTTAGCAATGACAAGA
CGATGCTATATGTGAAGCTCTTCAAATTATCTTCTCCGCCATCGGAGCCAA
TGGCTCTGGGCTTCATGGAGATAAAATGCTCACTTCATACCTCCAGAGATT
CTCAAACAGTCAACTGTCTTGGCATTAAACAGCTCGTGAACCTCTCAACTATT
TCCTTTTGCTTCGTGCAATTGTTCCGCAGTATTGGTGGTGGCGCTCAGGATAT
TTTGATGGAAAGTTCCTGCAGTTACTGCCAAATCTTCTTCAATTCTTGAATA
AATTGACGGTGAGTTTCATTTTTTGATATATCGGTAATACACTAAAAATCCAG
AATCTTCAGTCATGTCAACATCGGATTCAAATGCGTGAGCTCTTCGTGCGAGT
TGTGTTTGACTGTGCCAGTTCGACTCAGTTCCCTTCTGCCATACCTACCGCT
TCTGATGGATCCACTGGTGTGTGCGATGAATGGGAGTCCGAACATAGTTAC
ACAAGGATTGAGAACATTGGAATTATGTGTGGATAACTTGCAACCTGAATAT
CTTCTCGAAAATATGCTTCCTGTCCGTGGAGCTTTGATGCAAGGCCTCTGG
CGTGTTGTATCGAAAGCTCCAGATACATCATCGATGACAGCAGCGTTCAGG
ATCCTCGGAAAGTTCGGAGGAGCCAATCGAAAACCTTCTGAATCAACCGCAA
ATTCTTCAAGTAGCCACTTTAGGCGACGTAAGTTTATTTAGTTTATTCTCTTC
CTCGTTTTAAGTTCTAACATTGATCCTATTAACAGACTGTTGAGTCGTACATC
AATATGGAATTCTCGCGGATGGGACTCGATGGCAATCACAGCATTACCTG
CCACTGTCCGAGTTGATGAGAGTCGTTGCCGATCAGATGAGATATCCAGCT
GATATGATCCTTAATCCAAGTCTTGAATGATCCCGTCAACTCATATGAAGA
AATGGTGTATGGAATTGTGCAAGCCGTCTTGTTAGCCGGACTTGGATCTTC
AGGAAGCCCAATTACTCCAAGTGCAAAATCTTCCGAAGATTATCAAGAACTT
CTTGAAGATTTTGATCCAAACAATCGTACCCTGAAGTATACACATGTCCGA
GGGAAAGTGATCGAGAGCTTTTTGTGAATGCACTTCTCGCAATGGCTTGTA
GTTCTTAAGTTCTTTCTCTAATCAGATCTATATTTTAAATTTTTCAGACGG
AATATGGAATAAAGACGGTTTCCGGCATGTCTATAGCAAATCTTTATCAA
GTTCTCCGCCAGTTTGCGTTGATTGGAGTACTCGAATACATTGGTGGAAATG
GATGGATGCGTCATGCAGAAGAGGAAGGTGTTCTACCATTTGTCCTTGACT

12/92
FIGURE 8

CGTCTGTTATGGTTGATGCTCTGATTATTTGTCTCTCTGAAACATCGTCAAG
CTTCATCATTGCTGGTGTCTCTCTCGTCATATCAATGAGACTCTCTCG
CTTACACTTCCCGATATTGATCAAATGTCGAAAGTTCCAATGTGCAAATAGTT
GATGGAGAAGGTGTTCAAATTGTGTACGGGCTGCTTGGTATGCAAGATC
TGGTGGAAATCAATGCAATTGGATACATGATCGAATCGTTTCCACGAAAATTT
GTTATGGACTTTGTGATAGATGTTGTTGATTGATCATGGAAGTTATTTTGG
GAACTGTTGAAGAAATATCAAGTGGATCTGCTGATTCTGCATACGATTGTCT
CAAGAAAATGATGCGAGTCTATTTTCATCAAAGAAGAAGGCCAAGAAGAGGA
GAATCTGACACTCGCGACTATTTTTGTGTCTGCAATCTCTAAGCATTACTTCC
ACAGTAATGAAAGAGTCAGAGAATTTGCGATTGGTTTAATGGATCATTGTAT
GGTTCACTCAAGACTTGACCATCCCTTGATAAGTTCTACTATCGATTCAAG
GAGTTCTTTGAGCCAGAATTAATGCGGGTGCTCACAACAGTTCCAACAATGT
CATTGGCAGACGCAGGAGGAAGTTTGGATGGAGTTCAAACTATATGTTCA
ACTGTCCGGATGGTTTTGATTTGAAAAAGATATGGACATGTACAAGCGATA
TTTGTACATCTGCTGGATATTGCACAAACCGATACATTTACCTTAAACCAA
GGAATGCCCTTCAAAAAATGCGAGACATGCCCATCGCATTTCCTTCTCCATT
CCCAATCACTACACATATTGATTCAATGCGAGCCAGTGCTCTACAGTGTCTT
GTGATCGCGTATGATCGAATGAAGAAGCAATACATCGACAAGGGAATAGAG
CTGGGTGATGAGCATAAGATGATAGAGATCCTCGCACTTCGCAGCTCCAAG
ATCACAGTTGATCAAGTCTACGAGAGCGATGAATCTTGGAGACGATTGATGA
CAGTTCTATTGAGAGCAGTCACTGACAGAGAACTCCTGAAATTGCGGAGA
AGCTTCATCCTTCACTTTTGAAGGTCTCACCAATATCCACAATCATCATCGCA
ACATTTGGTGCTTCTTACATAAGAAATATTAGTGGAGCAGGAGATGACAGTG
ATTCAGATCGTCATATTTCTGACAACGATATAATGAAGTTCAAGTGTCTCGTG
GAGCTCAATCCAAAGATTCTGGTCACAAAAATGGCAGTGAATCTCGCAAATC
AAATGGTTAAATATAAGATGAGTGACAAGATCTCTAGGATTTTGTGAGTTCC
CAGTAGCTTCACTGAAGAGGAGCTCGATGATTTTGAAGCGGAGAAGATGAA
AGGAATTCGAGAGTTGGATATGATTGGTCATACGGTTAAAATGCTTGCTGGA
TGCCCAAGTGACCACATTCACGGAGCAAATTATTGTGGATATCAGTCGTTTTG
CTGCTCATTITGAGTATGCTTATTCGCAAGATGTACTTGTAATTGGATTGAT
GATGTCACAGTAATCCTCAACAAAAGTCCCAAAGATGTATGGAAGTTCTTCT
TGTCTCGAGAATCAATTCTAGATCCTGCACGCAGATCCTTTATTGGAAGAAT
CATAGTCTATCAATCAAGTGGTCCACTGCGACAGGAATTCATGGATACTCCG
GAATATTTTGAAGAACTCATTGATCTTGACGATGAGGAGAATAAGGATGAAG
ATGAGAGAAAAATCTGGGATCGTGATATGTTTGCATTTTCGATTGTGATCG
TATCTCGAAGAGCTGCCCTGAGTGGCTTATTTCTCCGAATTCCCCAATTCCA
AGAATTAAGAAGTTGTTCTCCGAAACGGAATTCATGAGCGATATGTGGTTC
GAGCATTGACTGAGGTGAAGAAATTTCAAGAAGAGATCATAGTGAAACGGA
TGACAGAGCACAAGTACAAGGTTCCGAAGCTGATTCTGAATACCTTCTGA
GATATTTGAGGTAATTTCAAGATAGTTTGTAAAAATTAATTACAAAGAAATATA
CCAAAATGAACCCCAAAAAAATTTTTGAATTTTCGGATCAAAAAAATTTAA
TATTTTCTCGAAAAATCCTTCAAAATACCAAAAAATTCGAATTCCTCACTTCTAA
AATTATTTTGAATTTTAAATAATTTTTGAACATTTCTCTATGAAATTCATGTT
TTGGGCTATTTCAAGGCTATAAAAAATTTTTTCTGATTTTAAATAACTTGCAA
ATTCAGGCTCAACATCTATGACTACGATCTATTCATCGTTATCGCCTCGTGT
TTCAATGGCAATTTCTGCACCGATCTCTCTTTTCTTCGCGAATATCTTGAAAC

13/92
FIGURE 8

TGAAGTCATCCCGAAAGTGCCGTTACAATGGCGGAGAGAGCTGTTTCTTCG
AATTATGCAGAAGTTTGATACGGATCCACAACTGCTGGAACAAGTATGCAG
CATGTGAAGGCCCTTCAATATTTGGTTATTCCCACGTTGCATTGGGCGTTCCG
AGCGATATGATACGGATGAAATTGTTGGCACCGCACCAATAGATGATTCGG
ATTCTTCGATGGATGTAGATCCGGCAGGCAGCTCGGATAACCTTGTGGCTC
GTTTAACATCAGTCATTGATTCTCATCGTAATTATCTGAGCGATGGAATGGT
CATTGTTTTCTATCAACTTTGCACATTGTTCTGTACAAAACGCCTCCGAACATA
TTCACAATAATAACTGCAAGAAACAAGGTGGACGCCTACGGATCCTGATGCT
CTTCGCCTGGCCGTGCCTGACCATGTACAATCATCAAGATCCAACAATGCG
GTACACTGGATTCTTCTTCTTGGCCAATATTATAGAGCGTTTCACAATTAATC
GGAAAATCGTGCTTCAAGTGTTCCATCAACTTATGACTACTTATCAGCAGGA
CACTAGAGATCAAATCCGGAAAGCCATTGATATATTAAGTCCAGCTTTGAGG
ACACGAATGGAAGATGGACACTTGCAAATATTGAGTCATGTGAAGAAAATTC
TTATCGAAGAATGCCATAATTTGCAACATGTTTCAGCATGTTTTGTAAGTTTAT
TATCTAAAATGATTTTTTTTTAATGTTAAAAATTTAATTTTAAAATGCGTTCGTG
CTCCTTTAATAATTCCTGAATTTCCAGCCAAATGGTGGTTCGCAATTATCGT
GTCTACTATCATGTTTCGATTGGAGCTTCTCACGCCTCTTCTGAACGGAGTTC
AACGAGCACTTGTGATGCCAAATAGTGTTCTGGAAAAGTAAGTTTCCAGCCC
GTTGTTTCGTAAACTCACCCCTTGTAATATTTAGCTGGCAAACCTCGACGTCA
TGCGGTGGAGATCTGCGAGATGGTCATCAAGTGGGAATTGTTTCAGAACGCT
GAAAACAGATCATATTATCAGTGACGAAGAAGCTCTCGAAGTTGACAAGCAA
TTGGATAAGCTGCGAACAGCTTCATCCACAGATCGTTTCGATTTTCGAGGAG
GCTCATAACAAGAGAGACATGCCTGATGCTCAACGCACGATTATCAAAGAG
CACGCCGATGTGATTGTCAATATGCTTGTCCGATTCTGTATGACGTTCCATC
AGAATTCGGGTTCTTCGTCCACTTCTCAAAGTGGGAACCATGGTGTGAGTT
GACCAAAAAATGTCAGCTGCTTCTACGTGCAGCCCTACGACCAAGCATGTG
GGGAGAATTTGTCAGCTTCCGATTAACAATGATCGAAAAGTTTTTGTCAATT
CCGAATGATAATGCTCTACGCAATGATATAAGTTCTACGGCCTACGCTAATA
CTATCCAAAATGCACAACACACTCTGGATATGCTGTGTAATATTATTCCTGTT
ATGCCAAAACTAGCTTGATGACTATGATGAGACAACTCCAACGGCCACTCA
TACAATGTCTCAATAACGGAGCTCAGGTATGTGAAGAACGATGAATAGGGG
GTTATAAATCACTAATTTCTCTTAGAACTTTAAGATGACTCGTCTTGTCCTC
AAATTGTCAGTCGGTTACTCGAAAAGACAAATGTTTCGGTTAACGGGGCTTGA
TGAGCTGGAGCAATTGAATCAATACATTTCCCGATTCTACATGAACATTTT
GGATCTCTTTTGAAGTAAGTTTTATTTTGAATTTCCATCTTTCAACCCCTTCGC
CAGTTGCAGAACTTGAGTGGACCAGTGTTGGGAGTTCTCGGAGCATTTTC
TCTTTTCCGAACAATTTGTGGACACGAGCCAGCATACTTGGATCATTTGATG
CCTTCATTTGTAAAAGTGATGGAGAGAGCTGCAAAAGAGCACTTGGCGTAT
GTTGCCAACTCGCAAGATGGAAATATGGTGAAGAGTAAGTTCTATAAAAAGA
TTCAGATTTTCTAATCCCTTAGATTCTTTCCAGATGTTGCTGAATTGTTGT
GTGCATGCATGGAGCTGGTACGTCCCAGAGTCGATCATATCAGTATGGAGA
TTAAGAGATCAATTGTTGGTGGTATTATCGCGGAGCTGATTATCAAATCGAA
TCACGATAAGATCATCCAGACGTCAGTGAAGCTTCTCGGAGCAATGATTAG
CACGCAGGATATGGAATTTACAATTCTCACTGTTCTTCCGCTACTTGTTCTG
ATCCAATCAATTATTGTGACCAAGTTCAAGAATTGCAAGGATCTGATAGCAG
ACTATCTTGTGTGGTTATTACCGTTTTTGGAGAACAGCGAATATCGGAACTC

14/92

FIGURE 8

GGAAGCTGGATCTCGTCTCTGGGAAGGATTCTTCTGGGGAAGTCAAGAGTAG
CGATCCTCAAACCCGGGAGAAATTCTCGATAGTTTGGGAGAAGACTTGGCC
ACACATGGCAACAGTAGATATTGCTCATCGAATGAAATATATCATGCAAAAT
CAAGATTGGTCCAAGTTCAAACACGCGTTTTGGTTGAAATTCGCACTTTGGG
GAATGCTACGAACGATTGCCAAACGGCCAAGTATCCGAATAATAAGAGAA
AGAAAGTGATACTGTTGAACTGTGCAACTCCATGGAGAACAATTGAATATGC
AGCGAAATTGAAGGATCAGCCAATGGAAGTGGAAACTGAAATGAAACGAGA
AGAGCCAGAACCGATGGAAGTTGACGAAAAAGACTCGCAAGATGATTCTAA
GGATGCCGGAGAGCCCAAGGAGAAGGAAAAGCTCACATTGGAATTATTGCT
TGCTGGACAACAAGAACTTTTGGATGAAGCTTCCAATTATGATTTTGCGGAT
GCTCTAGATACAGTATCCCAGATTACATTTGCACTTAATGGTAAATTGTTCAA
AGTTTATGAATATTTTTCTTAAAAATCACATTTTCAGAGAATCAAGTGACAA
GCAAGATGTGGGTAGTGTGTTCAAATCATTCTGGAGTTCCTTATCACAAATC
CGAAATCGAAGATTTACGGCGCTAGTCGTTCCGTTTATGAGCAGTGGAGT
GCATAATAATTATCAGACGGGTGTACAGGATAGTGTGCTTGCTGTTTGGCTT
GAAGCTGTTGGTGACGCTGTTCAATTTGCCGTCCAGATTGATTGAGGTACGTT
CTGAAAATGAATGCTGGAAAAAATTCGATTTTCTGTTTAAAAAAGTTAAAA
TTTCCGATTTTTTGAATAGCAAAAAAAGAAAAACATTTATTTTGA AAAAAGA
GTCCTCACCGGAATTTTTTAATAATAAATTTAAAAAAGAAAAAAACTAAA
AACTTCAATTTTTGAAAATCAAAAAAATTTACAGAAACAGACGAGGTAAAA
AATTTTAAAAAAGTTCTGTAAAAAATGGAGAATCACAGTTTTCGTTGTCTT
TTCTGAAAAAATTTGAAAAATTA AAAATTAACGATTTTTTGGTTTTTAATTTA
AAAAATATACGAAAAAAGACTGAAGAATTTTTTGTCAAAAAAATTTGATT
TTGATGAGGGAAAAAGTTCAAAAACCTTGGAGAAATCATCGGAAATTTTAGAA
GATTCAATAAAAATTTCCAAAAAATTTGAACATTTATGATTTTTGGGTAT
TTTGAAAAATTGAAAAATTACGCTTAATTTTTAGATTAAAAAATCAAAAAA
ACCAACACTCCTTTTGAAACTTGACACTTTTGAAACGTTTTTTTTTTTGAAT
AATAAATTTCTCATTTTCAGTTTATCTCATCAAAACACGAATGCTGGCATAACG
GAATCAGGCTTCTCGAGAATCATATATGGACAATTCCAAAGCAACTCAACAA
CACGTTACTCCGAGAAATGAAAGTGGCACCAGGTCTCGCTGGAGATATTGA
GACACTCGAATCTCTTGGAACTCTACAATGAGATATCAGAGTTTGATCAG
TTGCTGCAATCTGGGAACGCGTGCTGTATTTCTGATACGATGAGAGCA
ATGTCAGCTATGCAATTGGGAGATATGGAATTAGCTCAATCTTATCTGGAAA
AATCAATGAGCAGTACGTATGAACTCTTGCTCCGACAATCAATCGTAAGTT
TGGATCAATCGGTTGTACTTCTCACACAAAATAGTATTCCTTTCAGCAAACAA
CACTTCAAATTCGGAGAAGCATGTTTCTCCGATTATTGACAAAGAATACGAT
CATTGGATGGAGATGTACATCACAAATTGCTCGGAGCTTCTTCAGTGGCAAA
ATGTGGCCGACGTATGCAATGGCAAAGACATGCAACATGTTGCTGGCCTGA
TCAACGCAGCATCTCACATTCCGGACTGGAATGTGGTTCGAGGAGTGTA AAA
GTCAGATAGCTGGATGTATTCCACCAAGTTTCCATTTAGATTACACTCTTTTC
AATTTGATGAGTACTGTTATGGTTAGTTTAAAGTCAAAAAGTGATATATAATTA
TTGTTTAAATTTTTCAGCGAATGAATGAAACTCAAGCCCGACACATATGAAG
GAACGATGCAAAATTGCAATTCAAGAGTGCACAGAAGCTCATATTAGTCGTT
GGAGAGCACTTCCGTCAGTTGTTTCATATGGTCATGTCAAGATTCTTCAGGC
AATGAAGTTGGTTTCGAGAAATTGAAGAGTCTACAGATATTTCGATTGCTCTG
CTCGAGGCCCATCAAACAAAGTGGATCAGGCGTTGATGGGCGATATGAAG

15/92

FIGURE 8

GGAAGCTGGATCTCGTCTCTGGGAAGGATTCTTCTGGGGACTCAAGAGTAG
CGATCCTCAAACCCGGGAGAAATTCTCGATAGTTTGGGAGAAGACTTGGCC
ACACATGGCAACAGTAGATATTGCTCATCGAATGAAATATATCATGCAAAAT
CAAGATTGGTCCAAGTTCAAACACGCGTTTTGGTTGAAATTGCGACTTTGGG
GAATGCTACGAACGATTGCCAAACGGCCAACTGATCCGAATAATAAGAGAA
AGAAAGTGATACTGTTGAACTGTGCAACTCCATGGAGAACAATTGAATATGC
AGCGAAATTGAAGGATCAGCCAATGGAAGTGGAACTGAAATGAAACGAGA
AGAGCCAGAACCGATGGAAGTTGACGAAAAAGACTCGCAAGATGATTCTAA
GGATGCCGGAGAGCCCAAGGAGAAGGAAAAGCTCACATTGGAATTATTGCT
TGCTGGACAACAAGAACTTTTGGATGAAGCTTCCAATTATGATTTTGGCGAT
GCTCTAGATACAGTATCCCAGATTACATTTGCACTTAATGGTAAATTGTTCAA
AGTTTATGAATATTTTTCTTAAAAATCACAATTTTCAGAGAATCAAGTGACAA
GCAAGATGTGGGTAGTGTTGTTCAAATCATTCTGGAGTTCCTTATCACAATC
CGAAATCGAAGATTTACGGCGCTAGTCGTTCCGTTTATGAGCAGTGGAGT
GCATAATAATTATCAGACGGGTGTACAGGATAGTGTGCTTGCTGTTTGGCTT
GAAGCTGTTGGTGACGCTGTTTCAATTTGCCGTCCAGATTGATTGAGGTACGTT
CTGAAAATGAATGCTGGAAAAAATTCGATTTTTCTGTTTAAAAAAAGTTAAAA
TTTCCGATTTTTTGAATAGCAAAAAAAAAAAGAAAACATTTATTTTGA AAAAAGA
GTCCTCACCGGAATTTTTTAATAAATAAATTTAAAAAAAGAAAAAAAAGTAAA
AACTTCAATTTTTGAAAATCAAAAAAAAAAATTACAGAAACAGACGAGGTAAAA
AATTTTAAAAAAGTTCTGTAAAAAAATGGAGAATCACAGTTTTCGTTGTCTT
TTCTGAAAAAATTTGAAAAATTA AAAATTAACGATTTTTTGGTTTTTAATTTA
AAAAAATATACGAAAAAAGACTGAAGAACTTTTTTGTCAAAAAAAGTGAAT
TTGATGAGGGAAAAAGTTCAAAAACTTGGAGAAATCATCGGAAATTTTAGAA
GATTCAATAAAAATTTCCAAAAAATAAATTGAACATTTATGATTTTTGGGTAT
TTTGAAAAATTGAAAAATTACGCTTAATTTTTAGATTAAAAAATCAAAAAAA
ACCAACACTCCTTTTGAAACTTGACACTTTTGAAACGTTTTTTTTTTTGTCAAT
AATAAATTTCTCATTTTCAGTTTATCTCATCAAAACACGAATGCTGGCATACCG
GAATCAGGCTTCTCGAGAATCATATATGGACAATTC AAAGCAACTCAACAA
CACGTTACTCCGAGAAATGAAAGTGGCACCAGGTCTCGCTGGAGATATTGA
GACACTCGAATCTCTTGGAACACTCTACAATGAGATATCAGAGTTTGATCAG
TTGCTGCAATCTGGGAACGCCGTGCTGTATTTCTGATACGATGAGAGCA
ATGTCAGCTATGCAATTGGGAGATATGGAATTAGCTCAATCTTATCTGGAAA
AATCAATGAGCAGTACGTATGAAACTCTTGCTCCGACAATCAATCGTAAGTT
TGGATCAATCGGTTGTACTTCTCACACAAAATAGTATTCCTTTAGCAAAACAA
CACTTCAAATTCGGAGAAGCATGTTTCTCCGATTATTGACAAAGAATACGAT
CATTGGATGGAGATGTACATCACAAATTGCTCGGAGCTTCTTCAGTGGCAAA
ATGTGGCCGACGTATGCAATGGCAAAGACATGCAACATGTTGTTGGCCTGA
TCAACGCAGCATCTCACATTCCGGACTGGAATGTGGTCGAGGAGTGTA AAA
GTCAGATAGCTGGATGTATTCCACCAAGTTTCCATTTAGATTACACTCTTTTC
AATTTGATGAGTACTGTTATGGTTAGTTTAAGTCAAAAAGTGATATATAATTA
TTGTTTAATTTTTAGCGAATGAATGAAACTCAAGCCCGACACATATGAAG
GAACGATGCAAAATTGCAATTCAGAGTGCACAGAAGCTCATATTAGTCGTT
GGAGAGCACTTCCGTCAGTTGTTTCATATGGTCATGTCAAGATTCTTCAGGC
AATGAACTTGGTTGAGAAATTGAAGAGTCTACAGATATTGCGATTGCTCTG
CTCGAGGCCCATCAAACAAAGTGGATCAGGCGTTGATGGGCGATATGAAG

FIGURE 8

TCGTTGATGAAAGTATTCCGAAATAGAACACCAACCACTTCGGATGATATGG
GATTCGTTTCGACTTGGTATGATTGGAGGAATCAGATTCATGGAATGATGCT
TCAAAGATTCGAATATTGGGATAAAGTAGGACTCAACGTCGCTGCAACTGGA
AACCAGTCAATTGTTCCGATTCAATCAATGGCTCAAGCACAGTTGGCCGTAG
CCAAACATGCCAAGAATCTTGGATTCCATAATTTAACGAAAGATCTACTCAA
CAAATTAGCTGGATTGACAGCCATACCGATGATGGATGCTCAAGATAAAGTT
TGCACTTACGGCAAGACACTTCGCGATATGGCAAACAGTGCGGCTGACGAA
AGAGTGAAAAATGAGCTATTGTGTGAAGCGCTTGAAGTTTTGGAAGATGTGC
GAATTGATGATCTACAGAAGGATCAGGTTGCTGCATTGCTTTATCATCGTGC
TAATATTCATTCAAGTTCTTGATCAGTAAGTTTTCAATGCCGAAAAAAATTA
AGTTTTACAAAAATAAATTTAGAGCTGAAAATGCTGACTACACCTTCTCCGC
AGCCTCTCAACTTGTGCACTTGCAAATAGTGTGACAACCACTGGAATCAAG
CTCATGAAAAATTGGGGCCACCATCTTTACAAGAGATTCTTCTCTACGACAG
TTTGCAAGGAAACCGGAAACAACCTTCGGACGGCAGGCTCTCGCTTGTTACT
TCATTGCGGCTCGTGTGGATAACGATATCAAGGCGAGAAAACCGATTGCCA
AGATTTTGTGGCTCTCGAAGCACTTGAATGCGTGTGGATCACATGAAGTGAT
GAATCGGGTTATTAAGAAGCAACTTCATTCACTTAATCTCTTCAATTGGCTTT
ACTGGCTTCCACAATTGGTTACTGATGTTGATATAAACCAAATTCGAATTT
GTTCTGATTCTCTGCAAGGTAAGTTTTGAAATATTTAAATATTTTCAGAATTT
AAATGAAATTCATTTGCAGATGGCTGCTGCTCATCCACTTCAAGTATTTTACC
ACATTCGGGAGGCGAGTTAGCGTTGACGATATTGACTCGGTTCTCGAAGAAG
ATTACACTGATGAGCAAATGTCGATGGATGTTTCGGATGAGGATTGTTTTGC
AGACGATCCACCATTGATAGAATTCTGAAAATATGTCTGAAATATCGTCCAA
CTGATATTCGAGTCTTCCATCGTGTCTCAAAGAACTTGACGAGATGAATGA
GACATGGGTGAACGTCACCTGCGTCATGCGATCTGCCTCAAGGATCAGAT
GTTCAAAGATTTCTCGGAACAAATGGACGCGACGTTCAATGAGATGCAATAT
TCGGAGGATGTGACTATGATGACGTTGAGATGGAGGAAACAGCTGGAAGAA
GACTTGGTGTATTTCCAACAGAATTATAATCTTGATTTCCTGGAGATTGTA
CAAGCGAAAGATGATCGTGACGAAGGGATGTATGGGAGTCGAGAAAAGTCA
GATAATGTTGAAAAAGAGCTGAGTCAAGTGTTACAGAGCCGGCCGGCAT
GCAAGATGAATTTGATTTGTCACAAATATGACTAATATGATGGTCTCACAGT
TGGATATTCATGCAGTCGATGCTCCACGCCCTCAGGGATATATTCGTATTGT
TCTCGACTGGATTGAGCGATTGCTCGTCTGTTTCGATCGACTTCCACGAAG
AATCCCTCTGGAATCGTCAAGCCCATATCTCGCCAGATTGAGCCATCGTACA
GGATGCATCGAAATGCCATACGATTTGCTCAACGTTTTGCGCGCCAAGAAT
CATACTCTGATGGCTTCCAATCAAACGGGGCAATACATATCCATGCTCTCTC
GATTTGAGCCAACTTTGAGATTGTGATCAAAGGTGGTCAAGTGATAAGAAA
GATCTATATTCGAGGACAAACCGGAAAGAGTGCGGGCGTTTTATCTGAAGAA
ATCTGTGCAGGATGAGCCAACTAACCAGAGTTCCACAAATGTTCAAACATCTT
GATCAGCTTCTACAACCGATAGAGAGTCGGCGGAGAAGACATCTTCATGCT
CCAACAGTGCTGCAGATGAGAGTCGGACAGAAGACGACACTCTACGAAGTT
GCATCCGTTCAACCATATGCAATGCCACCGGATTGTACCAGAACTATCCAG
CATCACAATCGACATTGTTCCATCATATGATGTGCTGACTGCCACTTTCAAT
GGAAGTTATTATCCGGATGATATGGTATTGCACTTCTTTGAGAGATTCGCCC
AAAGTTCTTCATCCATCGGACAACCTCTTCCAACCTCCGACGAACCAAGATGG
AACAGTTGCTCCGCCACGACTAACGGAAGCTCACCACATCAAGAATATTATT

FIGURE 8

TATGAGTACGTTTGAGAAGCTAGTGTCTAAAATAATAATTAATGTAAAAAAT
TTTCAGAGACTTTGCCCGAGATATGATCCCATTCCGACTTCTCTAEGACTAC
CTCACTGCACGATATCCTGATCCGGTTATGTACTATGCAATGAAGAAGCAAT
TGCTGCACAGTCTCGCCGTCCTATCCACAATCGAATATCATTGCAATCTGAC
ACCAATGGGACCTGATCAAATGATGATGACAATGAATACTGGAGTCCTTAGC
AATCCTTCATATAGATTGAAATCCGAGGAGGACGATCACTTCATGATATTC
AACACTTTGGACATGAAGTTCATTCCGATTGACTCCAAATCTATCGATTTTG
GTTGGTGTTCACAGGATGGTGACTTGTTATGGAGTATGGCTGCTGCGTCA
AAATGTTTGATGAAGAAGGAACCTGAAGTTATCATGAGACCGTTAGTATGGG
ATGAATTCGCCAACAATACAGATTGCGACAAATCGGTAATTTTACTTTAATAT
GCTAATAGGGAATTGAACTAATGTTTTCCAAGCGTTTGCAGGTATTCGCGTG
TCATGCATCGAATTCTTACATCAATGGTGTGCGGAGCAAGCTTCGAAACACG
AATAGCGCCGACGCCAACTCAGAAAGGACGATTGTGTGTCGCTGATCAGT
CGAGCCAAGGATTCGGATAATCTGGCCCGAATGCCACCCACCTACCACGC
GTGGTTCTAGATCTCATAATTACCGTTCTCTATTTTGATCCCGCCTCCCACTC
TCACAGATCTCTATACATTTGTCAAATGTTTCCAAATCTTTTATCTGCCATA
CATTGTTTTTATTGTTTTGTTTCTTTTCTTTCTTTATTTCTTTTCTAACTTTA
AGATTTATGTAAATATTTAACTGCGCTGGTATTTATGAAAAATTCAGATAAAG
TTTTCAAGTTTAAAAAATCGAAAATTCGAAGTCGGAAGTTCTCTTACAGGTGT
AGTAAGTAGGCACAATGGCAATAGGTACATGGAAGGCTTGCGGAAGGCACA
TGGGTAGGCATAAGATCGAAAAATAAGCTGATATATAAATATAGATAGGTAT
TGTTAGGCACAAATTAGGCACGTAGGTGTGAGCTGGCAAATAGGTAGGCA
TGACGTTTCGGCAAATCGGCAAATTGCCGATTTGGCGAAAATTTTCAAATCCG
GCGATTTGCCGGAAATGTTTAGAGAAATTTTTTATAAGACAGAAAAACTTACA
ACTGTGTCTTTTTGAAATCTTCCGGTTTTCTTTATACAGTGCGTGCAACTTC
TATAGCGCCCCCCCCCCCCCCCCCCCCCTATTTTTTGCGGTTTCACGCC
ATTCTGATTTTTATTTTTCTGATTTTTTTTTTTTTTGCAGTGAACCTTGGCATTGA
GGATGCTTGGAGAGAAATATCAGCCAGCAAAATAAAGAATCTGGTCAACTCA
ATGTCGAATAGATTTTTGAGGTTATCGTTAAGAAGGGAGGTCCCACGACGT
ATTGATCCTTCATCGAGTTAACAATTATGATGTTTTAATTGATTTCAATCCAC
TTCTGGACACAGAAGGACGAATAGTGCAATCTGGTACAAGTTTATCACCACC
TACAACTTCGTCGATTTGTGGAAAATCTTTCAGACATGTCTCCATGAGTGTC
TCAGAACATCTTGGTCAGGTTTGGAGTCGATCCCACCGCTGGGAGCCGAGA
ATGGGCCTCTAACAC

FIGURE 9

itr-1 ORF sequence

ATGGATCCGGCTATGGCTTCTCCAGGCTATCGGTCTGTGCAGTCCGATCGG
AGTAATCACCTAACAGAGCTGGAAACGAGAATTCAAATCTTGCCGATAATT
CACAAAGAGATGATGTCAAATTGAAATGTTACAAGAGATTTGGAGCACAAAT
CGAAAATCATTTCACACTAAGTTCGCACGAGAAAGTCGTGGAGAGGGCTCATT
CTCTCGTTCCTACAAGTTTTCTGCAACACAAGTCCACAGTTCATTGCTGAAA
ACAATACACAACAGCTTCGAAAGTTAATGCTTGAAATCATTCTTCGACTTTTCG
AACGTAGAAGCCATGAAACATCATAGCAAAGAAATTATCAAGCAGATGATGA
GGCTAATCACCGTGGAAAATGAGGAGAATGCCAATTTGGCTATCAAATTTGT
CACCGATCAAGGGAGAAGTACCGGCAAAATGCAATATTGCGGAGAGGTTTC
ACAGATAATGGTCTCCTTCAAACAATGGTCATTGATCTGACGGCGAGTGGT
CGAGCTGGTGATATGTTCAACATAAAAGAGCATAAAGCTCCACCGTCAACTA
GCTCCGACGAGCAAGTCATCACTGAATATTTGAAGACTTGCTACTATCAACA
AACGGTTCTTCTCAACGGAACGGAAGGAAAACCGCCATTAAATACAATATG
ATTCCATCAGCTCATCAGTCAACGAAGGTGCTCCTGGAGGTTCCGTATCTC
GTGATTTTCTTCTATCAACATTTCAAACAGCGATCCAAACCGAAGCGCTTG
ATTTTCATGAGGCTTGGTCTTGATTTTCTAAATGTCAGAGTTCAGACGAGGA
TAAACTCAAACAAATCAAATAATAACCGATGATTTTGTGAGTGCACAGTCCC
GATTCCTGTCAATCGTCAACATTATGGCTAAGATTCCAGCGTTTATGGATCTT
ATCATGCAAATGGACCGCTTCTAGTGTCCGGAACAATGCAGATGCTCGAG
CGGTGCCCGGCTGATCTGATAAGTGTCCGACGAGAAGTTCTGATGGCTTTG
AAGTATTTACATCTGGAGAAATGAAGTCGAAATTTCTTCCAATGCTACCTC
GACTCATCGCTGAGGAGGTTGTTGTGGGAACAGGATTCATGCGATTGAGC
ATTTGCGAGTTTTTCATGTATCAAATGCTAGCAGATCTGTTGCATCACATGCG
AAATTCTATAGACTATGAAATGATCACACACGTGATTTTCGTATTCTGTGCA
CTCTTCACGATCCTAACAACCTCTTCTCAAGTCCAGATTATGTCTGCTCGGCT
GCTCAACTCACTGGCCGAATCTCTGTGCAAAATGGATTCACATGATACCTTT
CAGACTCGTGATCTGCTCATTGAAATCCTGGAGTCGCACGTGGCCAAAGCTC
AAAACCTTTGCAGTCTATCACATGCCTATTCTCTTCCAACAATACGGAACCG
AAATAGACTACGAATACAAAAGTTATGAGAGAGACGCCGAGAAACCTGGAA
TGAATATCCCAAAGGACACTATACGAGGAGTACCGAAACGAAGAATCCGTC
GGCTCTCCATTGATTCAGTTGAAGAGCTGGAATTCCTGGCATCAGAACCATC
CACGTCCGAAGATGCAGATGAGAGTGGTGGAGATCCGAACAAGCTTCCTCC
GCCAACAAAAGAGGGGAAAGAAAACGTCTCCCGAAGCGATTTTAACCGCCAT
GTCAACGATGACACCTCCTCCATTGGCAATTGTTGAAGCTCGAAATCTTG
AAGTATATAATGCATACGTGTAAATTCGTGACAGGACAATTGAGAATCGCCC
GGCCATCACAGGATATGTATCATTGTTGGAAGGAGCGAGATTTATTGGAACG
TCTTCTACGATATGGTGTAAATGTGTATGGATGTATTGCTGCTTCCAACAAC
CGAAATCAACCACAAATGCATTCTTCAATGCGGACAAAAGATGAGAAAGATG
CTCTGGAGTCTGTGGCAAACGTTTTTACAACAATCGACCATGCGATATTCCG
GGAAATCTTCGAAAAGTATATGGATTTCTTGATTGAAAGAATTTACAATCGGA
ACTATCCATTGCAATTGATGGTGAACACCTTCTTGTTTCGAAATGAAGTGCC
ATTCTTCGCATCTACGATGCTTTCATTCTTGATGTCTCGAATGAAATTGCTGG
AAGTTAGCAATGACAAGACGATGCTATATGTGAAGCTCTTCAAATATCTTC
TCCGCCATCGGAGCCAATGGCTCTGGGCTTCATGGAGATAAAATGCTCACT
TCATACCTCCCAGAGATTCTCAAACAGTCAACTGTCTTGGCATTAAACAGCTC

19/92

FIGURE 9

GTGAACCTCTCAACTATTTCTTTTGCTTCGTGCATTGTTCCGCAGTATTGGT
GGTGGCGCTCAGGATAATTTGTATGGAAAGTTCCTGCAGTTACTGCCAAATC
TTCTTCAATTCTTGAATAAATTGACGAATCTTCAGTCATGTCAACATCGGATT
CAAATGCGTGAGCTCTTCGTGAGTTGTGTTTGA CTGTGCCAGTTCGACTCA
GTTCCCTTCTGCCATACCTACCGCTTCTGATGGATCCACTGGTGTGTGCGAT
GAATGGGAGTCCGAACATAGTTACACAAGGATTGAGAACATTGGAATTATGT
GTGGATAACTTGCAACCTGAATATCTTCTCGAAAATATGCTTCCTGTCCGTG
GAGCTTTGATGCAAGGCCTCTGGCGTGTTGTATCGAAAGCTCCAGATACAT
CATCGATGACAGCAGCGTTCAGGATCCTCGGAAAGTTCGGAGGAGCCAATC
GAAAACCTTCTGAATCAACCGCAAATTCTTCAAGTAGCCACTTTAGGCGACAC
TGTTCAAGTCGTACATCAATATGGAATTCTCGCGGATGGGACTCGATGGCAAT
CACAGCATTACCTGCCACTGTCCGAGTTGATGAGAGTCGTTGCCGATCAG
ATGAGATATCCAGCTGATATGATCCTTAATCCAAGTCTGCAATGATCCCGT
CAACTCATATGAAGAAATGGTGTATGGAATTGTGAAAGCCGTCTTGTTAGC
CGGACTTGGATCTTCAGGAAGCCCAATTACTCCAAGTGCAAATCTTCCGAA
GATTATCAAGAACTTCTTGAAGATTTTGATCCAAACAATCGTACCACTGAAG
TATACACATGTCCGAGGGAAAGTGATCGAGAGCTTTTTGTGAATGCACTTCT
CGCAATGGCTTACGGAATATGGAATAAAGACGGTTTCCGGCATGTCTATAG
CAAATTCTTTATCAAAGTTCTCCGCCAGTTTGCGTTGATTGGAGTACTCGAA
TACATTGGTGGAAATGGATGGATGCGTCATGCAGAAGAGGAAGGTGTTCTA
CCATTGTGCCTTGACTCGTCTGTTATGGTTGATGCTCTGATTATTTGTCTCTC
TGAAACATCGTCAAGCTTCATCATTGCTGGTGTCTCTCTTCGTCATATC
AATGAGACTCTCTCGCTTACACTTCCCGATATTGATCAAATGTGAAAGTTC
CAATGTGCAAATACTTGATGGAGAAGGTGTTCAAATTGTGTACGGGCGCTG
CTTGGTATGCAAGATCTGGTGGAAATCAATGCAATTGGATACATGATCGAATC
GTTTCCACGAAAATTTGTTATGGAAGTTTGATAGATGTTGTTGATTGATCA
TGGAAGTTATTTTGGGAAGTTGGAAGAAATATCAAGTGGATCTGCTGATTC
TGCATACGATTGTCTCAAGAAATGATGCGAGTCTATTTTATCAAAGAAGAA
GGCCAAGAAGAGGAGAATCTGACACTCGCGACTATTTTTGTGTCTGCAATCT
CTAAGCATTACTTCCACAGTAATGAAAGAGTCAGAGAATTTGCGATTGGTTT
AATGGATCATTGTATGGTTCACTCAAGACTTGCACCATCCCTTGATAAGTTC
TACTATCGATTCAAGGAGTTCTTTGAGCCAGAAATTAATGCGGGTGCTCACAA
CAGTTCCAACAATGTCATTGGCAGACGCAGGAGGAAGTTTGGATGGAGTTC
AAAACATATGTTCAACTGTCCGGATGGTTTTGATTTGAAAAAGATATGGA
CATGTACAAGCGATATTTGTCACATCTGCTGGATATTGCACAAACCGATACA
TTTACCTTAAACCAAAGGAATGCCTTCAAAAAATGCGAGACATGCCCATCGC
ATTTCTTCTCCTCCATTCCCAATCACTACACATATTGATTCAATGCGAGCCAGT
GCTCTACAGTGTCTTGATCGCGTATGATCGAATGAAGAAGCAATACATCG
ACAAGGGAATAGAGCTGGGTGATGAGCATAAGATGATAGAGATCCTCGCAC
TTCCGAGCTCCAAGATCACAGTTGATCAAGTCTACGAGAGCGATGAATCTTG
GAGACGATTGATGACAGTTCTATTGAGAGCAGTCACTGACAGAGAACTCC
TGAAATTGCGGAGAAGCTTCATCCTTCACTTTTGAAGGTCTCACCAATATCC
ACAATCATCATCGCAACATTTGGTGCTTCTTACATAAGAAATATTAGTGGAG
CAGGAGATGACAGTGATTGAGATCGTCATATTTGATACAACGATATAATGAA
GTTCAAGTGTCTCGTGGAGCTCAATCCAAGATTCTGGTCACAAAAATGGCA
GTGAATCTCGCAAATCAAATGGTTAAATATAAGATGAGTGACAAGATCTCTA

20/92
FIGURE 9

GGATTTTGTGAGTTCCAGTAGCTTCACTGAAGAGGAGCTCGATGATTTGGA
AGCGGAGAAGATGAAAGGAATTCGAGAGTTGGATATGATTGGTCATACGGT
TAAAATGCTTGCTGGATGCCAGTGACCACATTCACGGAGCAAATTATTGTG
GATATCAGTCGTTTGTGCTGCTCATTGAGTATGCTTATTCGCAAGATGTACT
TGTAATTTGGATTGATGATGTCACAGTAATCCTCAACAAAAGTCCCAAAGAT
GTATGGAAGTTCTTCTTGTCTCGAGAATCAATTCTAGATCCTGCACGCAGAT
CCTTTATTGGAAGAATCATAGTCTATCAATCAAGTGGTCCACTGCGACAGGA
ATTCATGGATACTCCGGAATATTTGAGAACTCATTGATCTTGACGATGAG
GAGAATAAGGATGAAGATGAGAGAAAAATCTGGGATCGTGATATGTTTGCAT
TTTCGATTGTGCGATCGTATCTCGAAGAGCTGCCCTGAGTGGCTTATTTCTCC
GAATTCCTCAATTCCAAGAATTAAGAAGTTGTTCTCCGAAACGGAATTCAT
GAGCGATATGTGGTTCGAGCATTGACTGAGGTGAAGAAATTTCAAGAAGAG
ATCATAGTGAAACGGATGACAGAGCACAAGTACAAGGTTCCGAAGCTGATT
CTGAATACCTTCTGAGATATTTGAGGCTCAACATCTATGACTACGATCTATT
CATCGTTATCGCCTCGTGTTCATGGCAATTCGTACCGGATCTCTCTTTTC
TTCGCGAATATCTTGAACTGAAGTCATCCCGAAAGTGCCGTTACAATGGCG
GAGAGAGCTGTTTCTTGAATTATGCAGAAGTTTGATACGGATCCACAACT
GCTGGAACAAGTATGCAGCATGTGAAGGCCCTTCAATATTTGGTTATTCCCA
CGTTGCATTGGGCGTTGAGCGATATGATACGGATGAAATTGTTGGCACC
CACCAATAGATGATTGCGATTCTTCGATGGATGTAGATCCGGCAGGCAGCT
CGGATAACCTTGTGGCTCGTTTAAACATCAGTCATTGATTCTCATCGTAATTAT
CTGAGCGATGGAATGGTCATTGTTTTCTATCAACTTTGCACATTGTTGCTAC
AAAACGCCTCCGAACATATTCACAATAATACTGCAAGAAACAAGGTGGACG
CCTACGGATCCTGATGCTCTTTCGCTGGCCGTGCCTGACCATGTACAATCA
TCAAGATCCAACAATGEGGTAGACTGGATTCTTCTTCTTGGCCAATATTATA
GAGCGTTTCACAATTAATCGGAAAATCGTGCTTCAAGTGTTCCATCAACTTA
TGACTACTTATCAGCAGGACACTAGAGATCAAATCCGGAAAGCCATTGATAT
ATTAAGTCCAGCTTTGAGGACACGAATGGAAGATGGACACTTGCAAATATTG
AGTCATGTGAAGAAAATTCTTATCGAAGAATGCCATAATTTGCAACATGTTCA
GCATGTTTTCCAAATGGTGGTTGCAATTATCGTGTCTACTATCATGTTGAT
TGGAGCTTCTCACGCCTCTTCTGAACGGAGTTCAACGAGCACTTGTGATGC
CAAATAGTGTTCTGGAAAAATTTAGCTGGCAAACCTCGACGTCATGCCGTGG
AGATCTGCGAGATGGTCATCAAGTGGGAATTGTTGAGAAGCTGAAAACAG
ATCATATTATCAGTGACGAAGAAGCTCTCGAAGTTGACAAGCAATTGGATAA
GCTGCGAACAGCTTCATCCACAGATCGTTTCGATTTCGAGGAGGCTCATAA
CAAGAGAGACATGCCTGATGCTCAACGCACGATTATCAAAGAGCACGCCGA
TGTGATTGTCAATATGCTTGTCCGATTCTGTATGACGTTCCATCAGAATTG
GGTTCTTCGTCCACTTCTCAAAGTGGGAACCATGGTGTGAGTTGACCAA
AAATGTCAGCTGCTTCTACGTGCAGCCCTACGACCAAGCATGTGGGGAGAA
TTTGTGAGCTTCCGATTAACAATGATCGAAAAGTTTTTGTCAATTCCGAATGA
TAATGCTCTACGCAATGATATAAGTTCTACGGCCTACGCTAATACTATCCAA
AATGCAACAACACTCTGGATATGCTGTGTAATATTATTCTGTTATGCCAAA
AACTAGCTTGATGACTATGATGAGACAACCTCAACGGCCACTCATACAATGT
CTCAATAACGGAGCTCAGAACTTTAAGATGACTCGTCTTGTCACTCAAATTG
TCAGTCGGTTACTCGAAAAGACAAATGTTTCGGTTAACGGGCTTGATGAGCT
GGAGCAATTGAATCAATACATTTCCCGATTCTACATGAACATTTTGGATCTC

21/92

FIGURE 9

TTTTGAATTGCAGAACTTGAGTGGACCAGTGTTGGGAGTTCTCGGAGCATT
TTCTCTTTTGCGAACAATTTGTGGACACGAGCCAGCATACTTGGATCATTG
ATGCCCTTCATTTGTAAAAGTGATGGAGAGAGCTGCAAAAGAGCACTTGGCG
TATGTTGCGAACTCGCAAGATGGAAATATGGTGAAGAATTTCTTTCCAGATG
TTGCTGAATTGTTGTGTGCATGCATGGAGCTGGTACGTCCCAGAGTCGATC
ATATCAGTATGGAGATTAAGAGATCAATTGTTGGTGGTATTATCGCGGAGCT
GATTATCAAATCGAATCACGATAAGATCATCCAGACGTCAGTGAAGCTTCTC
GGAGCAATGATTAGCACGCAGGATATGGAATTTACAATTCTCACTGTTCTTC
CGCTACTTGTTGCGTATCCAATCAATTATTGTGACCAAGTTCAAGAATTGCAA
GGATCTGATAGCAGACTATCTTGTTGTGGTTATTACCGTTTTTGAGAACAGC
GAATATCGGAACCTCGGAAGCTGGATCTCGTCTCTGGGAAGGATTCTTCTGG
GGACTCAAGAGTAGCGATCCTCAAACCCGGGAGAAATTCTCGATAGTTTGG
GAGAAGACTTGGCCACACATGGCAACAGTAGATATTGCTCATCGAATGAAAT
ATATCATGCAAAATCAAGATTGGTCCAAGTTCAAACACGCGTTTTGGTTGAA
ATTCGCACTTTGGGGAATGCTACGAACGATTGCCAAACGGCCAACCTGATCC
GAATAATAAGAGAAAGAAAGTGATACTGTTGAACTGTGCAACTCCATGGAGA
ACAATTGAATATGCAGCGAAATTGAAGGATCAGCCAATGGAAGTGGAACT
GAAATGAAACGAGAAGAGCCAGAACCGATGGAAGTTGACGAAAAAGACTCG
CAAGATGATTCTAAGGATGCCGGAGAGCCCAAGGAGAAGGAAAAGCTCACA
TTGGAATTATTGCTTGCTGGACAACAAGAACTTTTTGGATGAAGCTTCCAATT
ATGATTTTGCGGATGCTCTAGATACAGTATCCCAGATTACATTTGCACTTAAT
GAGAATCAAGTGACAAGCAAGATGTGGGTAGTGTGTTGTTCAAATCATTCTGGA
GTTCTTATCACAATCCGAAATCGAAGATTTACGGCGCTAGTCGTTCCGTT
TATGAGCAGTGGAGTGCATAATAATTATCAGACGGGTGTACAGGATAGTGT
GCTTGCTGTTTGGCTTGAAGCTGTTGGTGACGCTGTTCAATTTGCCGTCCAG
ATTGATTGAGTTTATCTCATCAAAACACGAATGCTGGCATACCGGAATCAGG
CTTCTCGAGAATCATATATGGACAATTCAAAGCAACTCAACAACACGTTAC
TCCGAGAAATGAAAGTGGCACCAGGTCTCGCTGGAGATATTGAGACACTCG
AATCTCTTGGAACACTCTACAATGAGATATCAGAGTTTGATCAGTTCGCTGC
AATCTGGGAACGCCGTGCTGTATTTCTGATACGATGAGAGCAATGTCAGC
TATGCAATTGGGAGATATGGAATTAGCTCAATCTTATCTGGAAAAATCAATG
AGCAGTACGTATGAAACTCTTGCTCCGACAATCAATCCAAACAACACTTCAA
ATTCGGAGAAGCATGTTTCTCCGATTATTGACAAAGAATACGATCATTGGAT
GGAGATGTACATCACAAATTGCTCGGAGCTTCTTCAGTGGCAAAATGTGGC
CGACGTATGCAATGGCAAAGACATGCAACATGTTGCTGGCCTGATCAACGC
AGCATCTCACATTCCGGACTGGAATGTGGTCGAGGAGTGTAAGAGTCAGAT
AGCTGGATGTATTCCACCAAGTTTCCATTTAGATTACACTCTTTTCAATTTGA
TGAGTACTGTTATGCGAATGAATGAAAACCTCAAGCCCGACACATATGAAGGA
ACGATGCAAAATTGCAATTCAAGAGTGCACAGAAGCTCATATTAGTCGTTGG
AGAGCACTTCCGTCAGTTGTTTCATATGGTTCATGTCAAGATTCTTCAGGCAA
TGAAGTTGGTTCGAGAAATTGAAGAGTCTACAGATATTGCGATTGCTCTGCT
CGAGGCCCATCAAACAAAGTGGATCAGGCGTTGATGGGCGATATGAAGTC
GTTGATGAAAGTATTCCGAAATAGAACACCAACCACTTCGGATGATATGGGA
TTCGTTTCGACTTGGTATGATTGGAGGAATCAGATTCATGGAATGATGCTTC
AAAGATTCGAATATTGGGATAAAGTAGGACTCAACGTCGCTGCAACTGGAAA
CCAGTCAATTGTTCCGATTCATTCAATGGCTCAAGCACAGTTGGCCGTAGCC

22/92
FIGURE 9

AAACATGCCAAGAATCTTGGATTCCATAATTTAACGAAAGATCTACTCAACAA
ATTAGCTGGATTGACAGCCATACCGATGATGGATGCTCAAGATAAAGTTTGC
ACTTACGGCAAGACACTTCGCGATATGGCAAACAGTGCGGCTGACGAAAGA
GTGAAAAATGAGCTATTGTGTGAAGCGCTTGAAGTTTTGGAAGATGTGCGAA
TTGATGATCTACAGAAGGATCAGGTTGCTGCATTGCTTTATCATCGTGCTAA
TATTCATTCAAGTTCTTGATCAAGCTGAAAATGCTGACTACACCTTCTCCGCA
GCCTCTCAACTTGTGCACTTGCAAATAGTGTGACAACCACTGGAATCAAGC
TCATGAAAAATTGGGGCCACCATCTTTACAAGAGATTCTTCTCTACGACAGT
TTGCAAGGAAACCGGAAACAACCTTCGGACGGCAGGCTCTCGCTTGTTACTT
CATTGCGGCTCGTGTGGATAACGATATCAAGGCGAGAAAACCGATTGCCAA
GATTTTGTGGCTCTCGAAGCACTTGAATGCGTGTGGATCACATGAAGTGAT
GAATCGGGTTATTAAGAAGCAACTTCATTCACTTAATCTCTTCAATTGGCTTT
ACTGGCTTCCACAATTGGTTACTGATGTTGATATAAACCAAATTCGAACCTT
GTTCTGATTCTCTGCAAGATGGCTGCTGCTCATCCACTTCAAGTATTTTACC
ACATTCGGGAGGCAGTTAGCGTTGACGATATTGACTCGGTTCTCGAAGAAG
ATTACACTGATGAGCAAATGTGATGGATGTTTCGGATGAGGATTGTTTTGC
AGACGATCCACCATTTGATAGAATTCTGAAAATATGTCTGAAATATCGTCCAA
CTGATATTCGAGTCTTCCATCGTGTCTCAAAGAACTTGACGAGATGAATGA
GACATGGGTTGAACGTCACTTGCGTCAATGCGATCTGCCTCAAGGATCAGAT
GTTCAAAGATTTCTCGGAACAAATGGACGCGACGTTCAATGAGATGCAATAT
TCGGAGGATGTGACTATGATGACGTTGAGATGGAGGAAACAGCTGGAAGAA
GACTTGGTGTATTTCCAACAGAATTATAATCTTGATTTCTTGAGATTCTGTAA
CAAGCGAAAGATGATCGTGACGAAGGGATGTATGGGAGTCGAGAAAAGTCA
GATAATGTTGCAAAAAGAGCTGAGTCAAGTGTTACAGAGCCGGCCGGCAT
GCAAGATGAATTTGATTTTGTACAAATATGACTAATATGATGGTCTCAGAT
TGGATATTCATGCAGTCGATGCTCCACGCCCTCAGGGATATATTCGTATTGT
TCTCGACTGGATTGAGCGATTGCTGCTGCTTTCGATCGACTTCCACGAAG
AATCCCTCTGGAATCGTCAAGCCCATATCTCGCCAGATTGAGCCATCGTACA
GGATGCATCGAAATGCGATAGGATTTGCTCAACGTTTTGCGCGCCAAGAAT
CATACTCTGATGGCTTCCAATCAAACGGGGCAATACATATCCATGCTCTCTC
GATTTGAGCCAACTTTGAGATTGTGATCAAAGGTGGTCAAGTGATAAGAAA
GATCTATATTCGAGGACAAACCGGAAAGAGTGCGGCGTTTTATCTGAAGAA
ATCTGTGAGGATGAGCCAACTAACCGAGTTCCACAAATGTTCAAACATCTT
GATCACGTTCTACAAACCGATAGAGAGTCGGCGAGAAGACATCTTCATGCT
CCAACAGTGCTGCAGATGAGAGTCGGACAGAAGACGACACTCTACGAAGTT
GCATCCGTTCAACCATATGCAATGCCACCGGATTGTACCAGAACTATCCAG
CATCACAAATCGACATTGTTCCATCATATGATGTGCTGACTGCCACTTTCAAT
GGAAGTTATTATCCGGATGATATGGTATTGCACTTCTTTGAGAGATTGCGCC
AAAGTTCTTCATCCATCGGACAACCTCTTCCAACCTCCGACGAACCAAGATGG
AACAGTTGCTCCGCCACGACTAACGGAAGCTCACCACATCAAGAATATTATT
TATGAAGACTTTGCCCGAGATATGATCCCATTCGACTTCTCTACGACTACC
TCACTGCACGATATCCTGATCCGGTTATGTACTATGCAATGAAGAAGCAATT
GCTGCACAGTCTCGCGGTGCTATCCACAATCGAATATCATTGCAATCTGAAG
CCAATGGGACCTGATCAAATGATGATGACAATGAATACTGGAGTCCTTAGCA
ATCCTTCATATAGATTGCAAATCCGAGGAGGACGATCACTTCATGATATTCA
ACACTTTGGACATGAAGTTCCATTCCGATTGACTCCAAATCTATCGATTTTG

FIGURE 9

GTTGGTGTTCACAGGATGGTGACTTGTTATGGAGTATGGCTGCTGCGTCA
AAATGTTTGATGAAGAAGGAACCTGAAGTTATCATGAGACCGTTAGTATGGG
ATGAATTCGCCAACAATACAGATTGCGACAAATCGCGTTTGCAGGTATTCGC
GTGTCATGCATCGAATTCTTACATCAATGGTGTGCGGAGCAAGCTTCGAAAC
ACGAATAGCGCCGACGCCAAACTCAGAAAGGACGATTGTGTGTCGCTGATC
AGTCGAGCCAAGGATTCGGATAATCTGGCCCGAATGCCACCCACCTACCAC
GCGTGGTTCTAG

24/92

FIGURE 10

TRR-1 protein sequence

MDPAMASPGYRSVQSDRSNHLTELETRIQNLDNSQRDDVCLKMLQEIWSTIE
NHFTLSSHEKVVERLILSFLQVFCNTSPQFIAENNTQQLRKLMLEIILRLSNVEAM
KHHSKEIKQMMRLITVENEENANLAIKIVTDQGRSTGKMQYCGEVSQIMVSFKT
MVIDLTASGRAGDMFNIKEHKAPPSTSSDEQVITEYLKTCYYQQTVLLNGTEGK
PPLKYNMIPSAHQSTKVLLVPYLVIFFYQHFKTAIQTEALDFMRLGLDFLNVRV
PDEDKLKTNQIITDDFVSAQSRFLSFVNIMAKIPAFMDLIMQNGPLLVSQTMQML
ERCPADLISVRREVLMAKYFTSGEMKSKFFPMLPRLIAEEVVLGTGFTAIEHLR
VFMYQMLADLLHMRNSIDYEMITHVIFVFCRTLHDPNNSQVQIMSARLLNSL
AESLCKMDSHDTFQTRDLLIEILESHVAKLKTAVYHMPILFQQYGTEIDYEYKSY
ERDAEKPGMNIPKDTIRGVPKRRIRRLSIDSVEELEFLASEPSTSEDADESGGDP
NKLPPPTKEGKTSPEAILTAMSTMTPPPLAIVEARNLVKYIMHTCKFVTGQLRIA
RPSQDMYHCSKERDLFERLLRYGVMCMDFVLPTTRNQPMHSSMRTKDEK
DAESLANVFTTIDHAIFREIFEKYMDFLIERIYNRNYPLQLMVNTFLVRNEVPFF
ASTMLSFLMSRMKLLEVSNDKTMLYVKLFKIIFSAIGANGSGLHGDKMLTSYLPE
ILKQSTVLALTAREPLNYFLLLRALFRSIGGGAQDILY.GKFLQLLPNLLQFLNKL
NLQSCQHRIQMRELFVELCLTPVRLSSLLPYLPLMDPLVCAMNGSPNIVTQG
LRTLELCVDNLQPEYLLNMLPVRGALMQGLWRVVSAPDTSSMTAAFRILGK
FGGANRKLNLNQPOILQVATLGDTVQSYINMEFSRMGLDGNHSIHLPLSELMRVV
ADQMRYPADMILNPSPAMIPSTHMKKWCMELSKAVLLAGLGSSGSPITPSANL
PKIIKKLLEDFDPNNRTTEVYTCPRESRELNVNALLAMAYGIWNKDGFRHVYS
KFFIKVLRQFALIGVLEYIGGNGWMRHAE EEGVLPLCLDSSVMVDALICLSETS
SSFIIAGVMSLRHINETLSLTLPDIDQMSKVPMCKYLMEKVFKLCHGPAWYARS
GGINAIGYMIESFPRKFVMDVDFIDVVD SIMEVILGTVEEISSGSADSAYDCLKKM
MRVYFIKEEGQEEENLTATIFVSAISKHYFHSNERVREFAIGLMDHCMVHSRLA
PSLDKFYYRFKEFFPELMRVLT TVPTMSLADAGGSLDGVQNYMFCNCPDGFDF
EKDMDMYKRYLSHLLDIAQTDFTLNQRNAFKKCETCPSHFLPPFPITTHIDSMR
ASALQCLVIAYDRMKKQYIDKGIELGDEHKMIEILALRSSKITVDQVYESDESWR
RLMTVLLRAVTDRETPEIAEKLHPSLLKVSPISTIIATFGASYIRNISGAGDDSDS
DRHISYNDIMKFKCLVELNPKILVTKMAVNLANQMVKYKMSDKISRILSVPSST
EEELDDFEAEKMKGIRELDMIGHTVKMLAGCPVTTFTTEQIIVDISRFAAHFEYAY
SQDVLVNWIDDVTVILNKSPKDVWKFFLSRESILDPARRSFIRRIIVYQSSGPLRQ
EFMDTPEYFEKLIDLDEENKDEDERKIWDRDMFAFSIVDRISKSCPEWLISPNS
PIPRIKKLFSETEFNERYVVRALTEVKKFQEEIIVKRMTEHKYKVPKLILNTFLRYL
RLNIYDYDLFIVIASCFNGNFVTDLSFLREYLETEVIPKVPLQWRRELFLRIMQKF
DTPQTAGTSMQHV KALQYLVIPTLHWA FERYDTDEIVGTAPIDDS DSSMDVDP
AGSSDNLVARLTSVIDSHRNYLSDGMVIVFYQLCTLFVQNA SEHIHNNNCKKQG
GRLRILMLFAWPCLTMYNHQDPTMRYTGFFFLANIIERFTINRKIVLQVFHQMT
TYQQDTRDQIRKAIDILTPALRTRMEDGHLQILSHVKKILIEECHNLQHVQHVQ
MVVRNYRVYYHVRLELLTPLLNGVQRALVMPNSVLEKFSWQTRRHAVEICEMV
IKWELFRTLKTDHIIISDEEAEV DKLRLTASSTDRFD FEEAHNKRDMPPDAQ
RTIIKEHADVIVNMLVRF CMTFHQNSGSSSTSQSGNHGVELTKKCQLLLRAALR
PSMWGEFVSFRLTMIEKFLSIPNDNALRNDISSTAYANTIQNAQHTLDMLCNIIIPV
MPKTSMTMMRQLQRPLIOCLNNGAQNFKMTRLVTQIVSRLL EKTNVSVNGLD
ELEQLNQYISRFLHEHFGSLLNCRNL SGPVLGVLGAFSLLRTICGHEPAYLDHL
MPSFVKVMERAAKEHLAYVANSQDGNMVKNFFPDVAELLCACMELVRPRVDHI

SMEIKRSIVGGIIAELIISNHDKIIQTSVKLLGAMISTQDMEFTILTVLPLLVRIOŠII
VTKFKNCKDLIADYLVVVITVFENSEYRNSEAGSRLWEGFFWGLKSSDPQTREK
FSIVWEKTWPHMATVDIAHRMKYIMQNQDWSKFKHAFWLKFALWGMLRTIAKR
PTDPNNKRKKVILLNCATPWRTIEYAAKLKQDPMEVETEMKREEPEPMEVDEK
DSQDDSKDAGEPKEKEKLTLELLLAGQQELLDEASNYDFADALDTSQITFALN
ENQVTSKMWWVLFKSFWSLSQSEIEDFTALVVPFMSSGVHNNYQTGVQDSV
LAWWLEAVGDAVHLPSRLIEFISSKHECWHTGIRLLENHIWTIPKQLNNTLLREM
KVAPGLAGDIETLESGLTYNEISEFDQFAAIWERRAVFPDTMRAMSAMQLGD
MELAQSYLEKSMSSSTYETLAPTINPNNTSNSEKHVSPIIDKEYDHWMEMYITNC
SELLQWQNVADVVCNGKDMQHVRLINAASHIPDWNVVEECKSQIAGCIPPSFH
LDYTLFNL MSTVMRMNENSSP THMKERCKIAIQECTEAHISRWRALPSVVSYG
HVKILQAMNLVREIEESTDIRIALLEAPSNKVDQALMGDMKSLMKVFRNRTPTTS
DDMGFVSTWYDWRNQIHGMMLQRFEYWDKVG LNVAATGNQSIVPIH SMAQA
QLAVAKHAKNLGFHNLTKDLLNKLGLTAIPMMDAQDKVCTY GKTLRDMANSA
ADERVKNELLCEALEVLEDVRIDDLQKDQVAALLYHRANIHSVLDQAENADYTF
SAASQLVDLQNSVT TGIKLMKNWGHLYKRFFSTTVCKETGNNFGRQALACY
FIAARVDNDIKARKPIAKILWL SKHLNACGSHEVMNRVIKKQLHSLNLFNWLYWL
PQLVTDVRYKPNSNFVLILCKMAAAHPLQVFYHIREAVSVDDIDSVLEEDYTDEQ
MSMDVSD EDCFADDPPFDRILKICLK YRPTDIRVFHRVLKELDEMNETWVERHL
RHAICLKDQMFKDFSEQMDATFNEMQYSEDVTMMTLRWRKQLEEDLVYFQQN
YNLDFLEIRNKRKMIVTKGCMGVEKSQIMFEKELSQVFTEPAGMQDEFDFVTN
MTNMMVSQLDIHAVDAPRPOGYIRIVLDWIRAIRRRFDRLPRRIPLESSSPYLAR
FSHRTGCIEMPYDLLNVLRANKHTLMASNQTGQYISMLSRFEPNFEIVIKGQVI
RKIYIRGQTGKSAAFYLKKSVD EPTNRVPOMFKHLDHVLQTDRESARRHLHA
PTVLQMRVGQKTTLYEVASVQPYAMP PDCTRNYPASQIDIVHPYDVL TATFNG
SYYPDDMVLHFFERFAQSSSSIGQPLPTPTNQDGT VAPPRLTEAHHIKNIIYEDF
ARDMIPFRLLYDYLTARYPD PVMYYAMKKQLLHSLAVLSTIEYHCNLT PMGPDQ
MMMTMNTGVLSNPŠYRFEIRGGRSLHDIQHF GHEVPFRLTPNLSILVGVAQDG
DLLWSMAAASKCLMKKEPEVIMRPLWDEFANNTDCDKSRLQVFACHASNSYI
NGVASKLRNTNSADAKLRKDDCVSLISRAKDS DN LARMPPTYHAWF

FIGURE 11

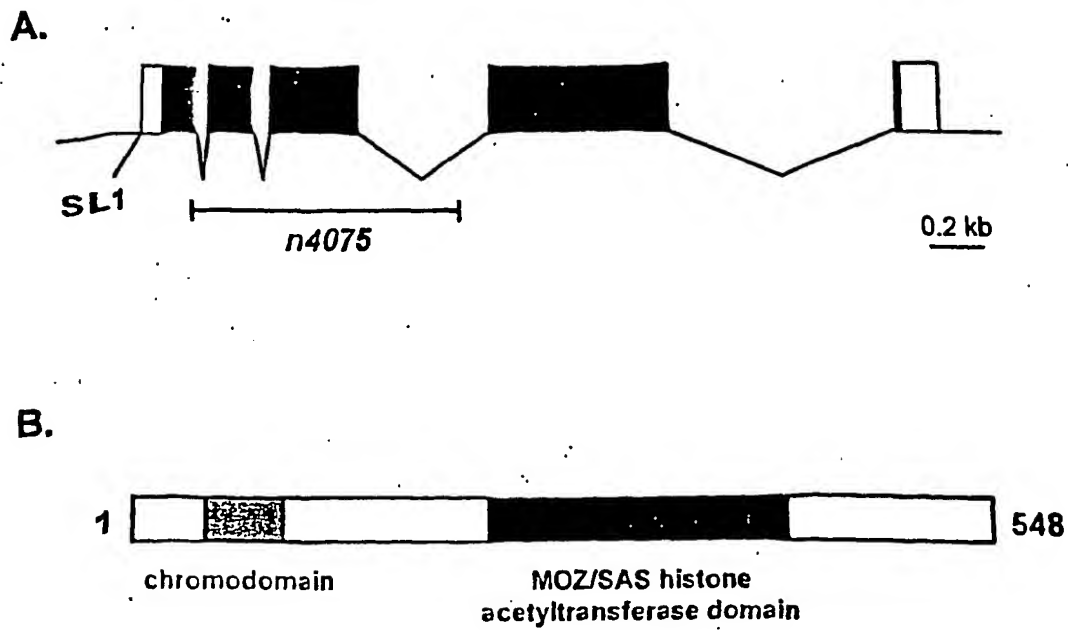
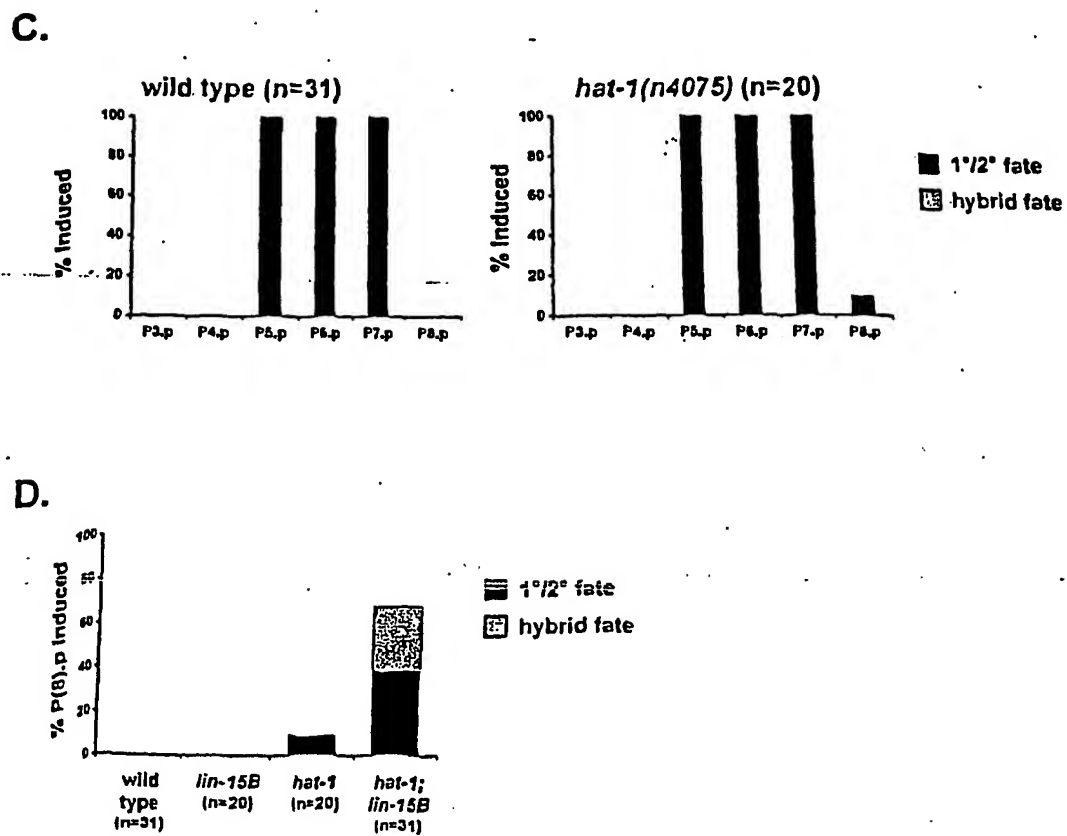


FIGURE 11B



hat-7 genomic sequence

TTGTTTTCGGATTTTTGTGTGCTTCGTAGTTGCTCCGATGATGCCGGATTG
AACATTTGAATGTAACATTTGAATTTTGAATTTGAAGGAATTCATTTGAATCTA
AAGCTTGCAGGGTCAAGACCGATACATTCTTGCAACACATGACTCGAAAGTA
TGTAGGAAAAATTGAAGTTGGAACTTGAATTTGATGAAAAAGTACAGTAA
TCCATTCTCTCTTATTTGCGAACTTTCTTCGATTTTGTATTTTCTAGATTTT
TTAAGCTAAAATTTTGTGTTTTATTTTCATTTTTCATGCTTTTCAATTTGCGTT
TTCAACAAAATTATGTTTTTCAGAGAAAATCTCGTGAACAATAACTCGGCTAC
TGTACCATTTAAAGGCGCAGACCTTTTCGCGCAGCATTGATTTAAATTTTTT
GTTCTGCGCTCAACAGTGCAATGGACATCTAGATATCTGAAATTTTACCACT
GAATTCAGTTCAATTTTTAAGCATCTTCAAAAATTTGCGTTTTCTTAATTTTCT
TGTGATCGTTTTTTTTTGAAGTACAATCGTACATTATAAATAACTATTTTTCT
AATTCGAATAATTTAATTCAGATCATTTGCGAAAATAATTGCCTTGAAACGT
TATGCCGCGGTCAATTTTCAACGACCCTTGTTATTCTTTTTTGAATTGCCGCC
CTTTTTCCCTGTGGCCGGCGCAGTGCGGCCGAGGTTGGTTTCTAGGCCAG
CCGGCGCGTTTATTTTTTTCGAGCATGATTTACAATTATTTCTTGCATTTTT
AAAGTTTTTATTGATAAAATAGTAAACTAACACGGATAATATTATTTAAA
ATTAAAAAACTAGTTTGTTTCATTTTTGGATCGATTTTAGATGTTGTTTCATGGA
TTATGCACGCAAGAAAGTACTATCGTTCACATTTGATTGCTATATTATTGAAT
ATTGAATTTTTCACACAAAATTGTACTATTTCCAGATATTTATCATGACCGAG
CCGAAGAAGGAGATTATAGAGGACGAAAATCATGGAATATCCAAGAAAATAC
CAACAGATCCCAGGCAATACGAGAAAGTTACAGAGGGATGCCGGTTATTGG
TCATGATGGCTTCACAAGAAGAAGAAAGTTAGTTTTTACATCTATTTAAACAC
ATTTTCCAATTATTTTCAGGATGGGCCGAAGTTATTTCAAGATGCCGAGCTG
CAAATGGTTCAATTAAATTCTATGTCCATTATATCGATTGCAACCGAAGACTT
GACGAATGGGTTCACTCTGATAGGCTCAATTTAGCGTCGTGTGAGCTACCA
AAAAAAGGAGGAAAGAAAGGAGCACACTTGCGGGAAGAAAAGTGAGAAATC
TATAAACTTTTCAAAGATTTTAAATAGTTTTATCAATTCATAATTATTTCACTC
GAGATTCGAATGAAAATGAAGGAAAGAAAAGCGGCCGAAAACGAAAGATTC
CACTACTTCCGATGGATGATCTCAAGGCGGAATCCGTAGATCCATTACAAG
CAATTTCAACGATGACCAGCGGATCTACTCCAAGTCTTCGAGGTTCCATGTC
GATGGTCCGCCATAGTGAAGATGCAATGACAAGGATCCGAAATGTCGAATG
CATTGAAGTAGGAAGATCACGAATTCAGCCATGGTACTTTGCACCTTATCCA
CAACAATTGACAAGTTTGGATTGTATTTATATTTGCGAATTTTGTCTGAAATA
TCTAAAGTCGAAAACCTTGCTGAAACGGCACATGGTGAGTGTTTCGAGTTAT
AGAAAATGACCGAATATAAATAACTGTTTTCAAATTCAAAATTTTCAATTTT
CCAAAATGAAAGAATCGGTGAATTCGAAAAAATTCGAGTTCTTGTTGTTTT
TGGCTGAATTTTTCGGTTTTTCTTGCTTTTTCCGTTGATATTAGTTTTGAAACA
ATGTTTTTAAATTTTTCCGGCATCGAAAAAATCGCAAATTCGGGAATTTGC
TCCAAAATTTGCATTTTTGAAATACTTTTTTTCGAAAACGAAAAAAAATTC
CAAACGGTGTTTCAAACCAAATTTATCGTAATCAAAAAAGTTTCGCAAATAGG
CCATTATTCTGCGTGGGAATTCAAATTAATAATCAGCTACTTTTTCTATTTTGC
AAAATGGAAAAAAACGTAAAAAATAGACAAATTTTAAATTTTTTAAACAATTA
CATTCGGTCCATACTCTTCATTTTCTATCATTTAATTAATAATGCCCAATTCTAA
TTAATTTTATTTTCAAGGAAAAATGTGCAATGTGTACCCACCTGGCAATCAAT
CTACAGTCACGATAAACTTTTCAATTTTTTGAATTCGACGGCCGCAAAAACAAA

FIGURE 12.

AGCTATGCTCAGAATCTATGCCTGCTTGCCAACTTTTTCTGGATCACAAGA
CTCTTTACTATGACACGGATCCATTTTGTCTATGTGCTAACCGAAGAAGA
CGAGAAGGGTCATCATATAGTTGGATACTTTTCAAAAGAAAAAGAATCAGCT
GAAGAATATAATGTTGCGTGTATTCTTGTTACCTCCATTTCAAAAGAAAGG
ATACGGAAGTTTGCTCATCGAATTCAGCTATGAACTCTCGAAAATTGAACAG
AAGACAGGATCACCCGAAAAACCACTATCAGATTTGGGACTTCTCTCATATC
GATCGTACTGGTCAATGGCCATCATGAAAGAGCTTTTCGCATTCAAAAGACG
ACATCCAGGCGAAGATATCACAGTTCAGGACATTTACAAAGTACATCGATT
AAACGAGAAGATGTTGTGTCAACGTTACAGCAACTTGATCTATACAAATACT
ATAAGGGATCATACATAATTGTGATTAGTGATGAAAAGCGTCAAGTTTATGA
GAAACGGATTGAGGCTGCGAAAAAGAAGACACGAATTAATCCAGCAGCTCT
GCAATGGCGACCCAAAGAGTACGGAAAGAAAAGAGTGAGTTTTTTTCAATCA
AAAATTCGTGTTTACGGCTAAAAACTGAAAATTAAATTAATTAATTCGTG
ATAACATTTTTTTTTCAAAAAACCAAAAAAAACAATTTCTGTTTTTGGCAGAAC
CAAAAAAAAATTTAAAAAAAACGGTTTACGCCCTATTTATACAAACAACA
GAAATTGCATTTTTTGAGCAAATTTGACCCTACAATTTTTTCCAGTTTTTG
CTCTTTTTCAAAAAAAACACCTAAACACTGGAAATACTAAATACTAAGGAAA
AAAATGGAAATACTGGTTTACAGTGTCAAAAAATTGAAATTTTCTAATAAAAT
CATTTTTCTTTTTACTAAATTTATCAAAAAATTTATAACTCAAATCTTTCAGTTTT
TGCGAATTTTTTTTCGAAAAAACGAAAAAAATAAACCTAATTTTAACCAAATT
GTAATTTTGAAAAATCTGGAACGTCCGGAAAACTGAAAAATTAAAAAAAAG
TTTTCAGAAATTTATTTTTAAAAAACCGTTTTTTTAAATCAAATTTTGTATATGT
TGATGAGAAAAAAAATAGAAATCAATGTTTTTAAGTTTTAAAAGAAAAATTTA
TTTTAATTATTTTAGTTTTAATAAGGTATTTAAACAGTAACAAGGATGTCGGTT
TTTCGATTTTCCGAAAACTAAAAAATTGTCTTTTTCGATTTTTTAATCGAAAA
AAAATAGAAATATTTTCACAAAACATACTATTCTTCTAAAAAAAAGATAGTG
GGAGATTTTAAATAATTTTGAACCTCTCGCAATTTTTTTCGAAATATCGAAAA
TCGAAAAACCGGCACAAAAGCAAAAAGTCTCCGGGAATATATCTTTAAATTA
TTTTATGAACTTTTTTTTTCAGGCGCAGATCATGTTCTAGCAACAACGACATGT
GTTCTCGCCACGACGATCTCAACCTGTACATTAAATATAACACTCCGTTTTTA
TCTCGCATCTACACACCGAAAAAGCTTACGCTATCCCTTTATCATTCCCACAC
CGCTCAGAGAGCGTACGCCTCATTTCATTTTATTGTTCTGTGTAATAATTTG
ACTTATTAGTCACTTATTTTTTTAATGAAATTATTCTTGAATTTATAATCTTCT
TGTTGCAGTTCAAATAATTAAATTCATCATATAGACAAGTAAGTTTATAACT
GCAAAAGTGAAGTTTTCTAATCATTAAAGCGTTCTGAAGATATTCGGCAACCG
CCTGAGCGATCAGATCACGGCGGGAACGAGTTGAGGCGTAGACATGCTTG
CAGCCAGTGACAACCTGAAAGATATTCAAAAAATTAATTTCAGGACTCGAAT
TTTTAACAATCTGAATAAAAAAATCCAAAATTGTATATTATAGAGTTTTTTGAA
ATCTAAGCGAAAGCGCGCTCCAATGTAAAACGAAAAGTGCTCCGCCCTTAA
ACGTTGGGTCCCGTTAGGAATTTGTTATTTTTTTCGGTTATTTCTGACTATATT
ATAATTTGAAACGACAAGTATTTTAAACATCATTTTCGACATAAAAAATATGT
AAAACAACAAAAACAATCGAAAAAATAGTGAAAAAGTTTGAATTTACAGTCT
CGCCGCCCTCCTACCGAGACCTAACGTTAGGAGGCGGAGCGTTTTCTTTGG
CATTGAAGCGCGCTTGCTGCGGCCCCATAATTAATAACTTACAGCCTTTGCA
AAGTCCTTCTTCTGTTTCATCCTCAATCTCGTCAATGTATTGATTGGACAACCT
CTCAATCTCGGACTGTTCCGCATTTTCATCCTTCAATTTTTTGATTGAGCCT

FIGURE 12

TGAATTGAGCCACCTTCTCCTCTCCGAAAGCCTTAACCGAATACTCCTTACA
AGCTTCTTTCAACTTGCCCTCGGCCTTCTCCTTGGCATCTC

FIGURE 13

hat-1 ORF

ATGACCGAGCCGAAGAAGGAGATTATAGAGGACGAAAATCATGGAATATCC
AAGAAAATACCAACAGATCCCAGGCAATACGAGAAAGTTACAGAGGGATGC
CGGTTATTGGTCATGATGGCTTCACAAGAAGAAGAAAGATGGGCCGAAGTT
ATTTCAAGATGCCGAGCTGCAAATGGTTCAATTAAATTCTATGTCCATTATAT
CGATTGCAACCGAAGACTTGACGAATGGGTTCAAGTCTGATAGGCTCAATTTA
GCGTCGTGTGAGCTACCAAAAAAAGGAGGAAAGAAAGGAGCACACTTGCG
GGAAGAAAATCGAGATTGCAATGAAAATGAAGGAAAGAAAAGCGGCCGAAA
ACGAAAGATTCCACTACTTCCGATGGATGATCTCAAGGCGGAATCCGTAGA
TCCATTACAAGCAATTTCAACGATGACCAGCGGATCTACTCCAAGTCTTCGA
GGTTCCATGTCGATGGTCCGCCATAGTGAAGATGCAATGACAAGGATCCGA
AATGTGCAATGCATTGAACTAGGAAGATCACGAATTCAGCCATGGTACTTTG
CACCTTATCCACAACAATTGACAAGTTTGGATTGTATTTATATTTGCCAATTT
TGTCTGAAATATCTAAAGTCGAAAACCTTGTCTGAAACGGGCACATGGAAAAAT
GTGCAATGTGTCACCCACCTGGCAATCAAATCTACAGTCACGATAAACTTTC
ATTTTTTGAAATCGACGGCCGCAAAAACAAAAGCTATGCTCAGAATCTATGC
CTGCTTGCCAACTTTTTCTGGATCACAAGACTCTTTACTATGACACGGATC
CATTTTTGTTCTATGTGCTAACCGAAGAAGACGAGAAGGGTCATCATATAGT
TGGATACTTTTCAAAGAAAAAGAATCAGCTGAAGAATATAATGTTGCGTGT
ATTCTTGTGTTACCTCCATTTCAAAGAAAGGATACGGAAGTTTGCTCATCG
AATTCAGCTATGAACTCTCGAAAATTGAACAGAAGACAGGATCACCCGAAAA
ACCACTATCAGATTTGGGACTTCTCTCATATCGATCGTACTGGTCAATGGCC
ATCATGAAAGAGCTTTTCGCATTCAAAGACGACATCCAGGCGAAGATATCA
CAGTTCAGGACATTTACAAAAGTACATCGATTAAACGAGAAGATGTTGTGTC
AACGTTACAGCAACTTGATCTATACAAATACTATAAGGGATCATACATAATTG
TGATTAGTGATGAAAAGCGTCAAGTTTATGAGAAACGGATTGAGGCTGCGA
AAAAGAAGACACGAATTAATCCAGCAGCTCTGCAATGGCGACCCAAAGAGT
ACGGAAGAAAGAGCGCAGATCATGTTCTAG

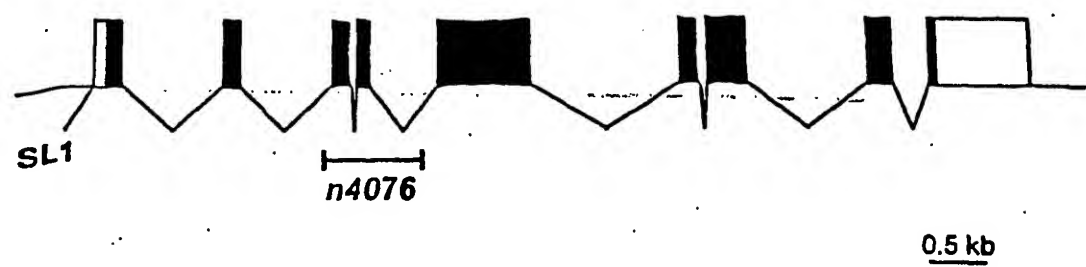
FIGURE 14

HAT-1 protein

MTEPKKEIIEDENHGISKIPTDPRQYEKVTEGCRLVMMASQEEERWAEVISR
CRAANGSIKFYVHYIDCNRRLEWVQSDRLNLASCELPKKGKKGAHLREENR
DSNENEGKKSGRKRKIPLPMDDLKAESVDPLQAISTMTSGSTPSLRGSMVM
GHSEDAMTRIRNVECIELGRSRIQPWYFAPYPQQLTSLDCIYICEFCLKYLKSKT
CLKRHMKEKCAMCHPPGNQIYSHDKLSFFEIDGRKNKSYAQNLCLLAKLFLDHKT
LYYDTPFLFYVLTEEDEKGGHHVGYFSKEKESAEYENVACILVLPPFQKKGYGS
LLIEFSYELSKIEQKTGSPEKPLSDLGLLSYRSYWSMAIMKELFAFKRRHPGEDI
TVQDISQSTSIKREDVVSTLQQLDLYKYYKGSYIIVISDEKRQVYEKRIEAAKKKT
RINPAALQWRPKEYGKKRAQIMF

FIGURE 15

A.

epc-1

B.

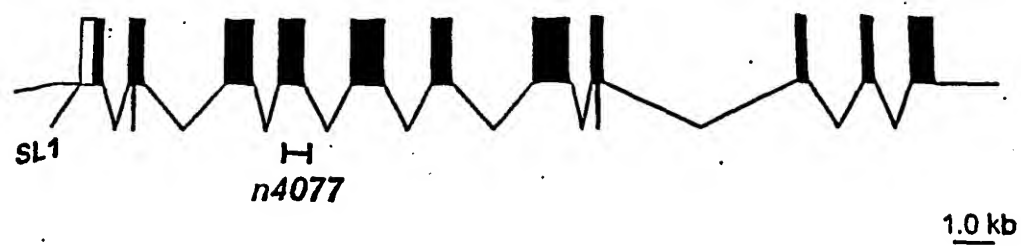
ssl-1

FIGURE 16

epc-1 genomic sequence

TTTCAAAAAAAAAAATTACCTCGTCAATTTCACTCTCCTCGATGCGATGATT
ATCCTCGTCCATTTTACCTGAAAAGTGTGATTTTTTACGAATAAAATTATTTT
CAGATACTTCTAGAAAAAAAAAACTGAACGGAATGTTACGAAATTAATTTTCA
AAGTTGCGAACTGAATTTTCGACAAAAAGTTTCACTGATATTCATTTCAAGC
ATATTGCAACGTTTTTAAATTAATTTCTAAGAGAAAAAACTGCAAAACAATTC
GAAAATAATTTTTACAAGTTACTTTTCGAAAAAGTAACAAAAATCCACTAATG
AACAGAAATTTTTGAACAAAAAGAGCTTCTCAGGCTATTTTTGGACGAATAT
TTTAATAAACTTTAAAAAATCAACGAAATCCCCTAAAAATCGCTGAAAAT
TCCAAAAATTAAAGTTCATTCTCGACCACACCTCTCGTAAATCAGCACGAGA
CTCACGCAACGCGACCGCGCCGCACTCAACGGCATTGAGTAATGCGGAGC
GGCAGCGTCGCGTCGTCTATTTGTGTGTGTGTGCGATTGTGTGTGGTGCGA
CGTGGCCGCTCTGTGTGCCTCTCTAGTGAGTGTTTTCCGACGAGAGACAAC
ACATTTTCGAGAGACGAAGAGAGTGGCGACGAGGAAGATAGTGTGGTAAGA
GGAGAGTGTGCGCGAGGGAAAGAGAGCAAAGTGTGAGTGTCTGTGAGAAG
AGAAGGAGACCCCCCCCCCCCCGCGCTCAACCAGTCGATAGTTGGCCTGA
GTGTAGGGCCTTCTGTTGTATTCCACTGCTAACCCCCCCCCAACACACAAAA
AGACTCAAAAAGTACTGCTTAAACACAGTGCTCAGCTCATTTTCATTTTTGAT
TTTTATGCTCGCCGTCATCGGCGGATGAATTCATCGCAAAGTCCGTGGCGA
TTCAACACGTGCGGCGTCTCGCCGCTCTTCTTAACCGTAGTTACAACGTG
GGAGTACAGAAAGATCGCCACTACTTCGAAGGCGTTTCGAGCCCGGGCGC
TCGACTCGAACCGGTCTATGACTGTATACTGGGGCCACGAACCTCCGGACC
TATCAGAATGCAGTGTTGGAAACCGGGCGGTGACACAAATGCCGTCTGGCA
TGGAAAAAGAAGAAGAACAGGTTGGTTTTTGGTGGATTATGGATTACTGCTC
CATTTTGAAATTTTCGAGTTTTAATGTCTTTTTTCGAATTCCTGGTGCTTTTT
TCTATCCGAATCATGTTTTAATTCGTTTTCCGACTACTTTGAAGAATTTTCA
AATTTTTGATCCCTGATGACGTCATAATTTTTGTCTTTGCCTTTCTGGATCGC
TTTTATAGTTATTTTCATTTTTTATTTCTTTTTTACACTTTTAACTTAACAATTC
TCTTAATTCATCCTATTCTATTTAATTTAAGTTTTGATTTTTGATTTTGATT
TTCTCTTTTCTTTTTAGCCGCCGGTGGGCCTTTATTACAACCTCTTAATCAT
AAAAAAATCAGTTTAAGCAGTTATACATAACTCTTATTATGAAAAATCGTTA
TTTTTCGACGGAACTTCATACTTTGAATTTATTTCCAATTTAGATTTTATTTT
CTCAAAGTCAGCTCAATTAACCTAACTTAAATGTTTTGTCTACCCGCAAAAT
GTTTTTTTTTAATATTTTAATTCATTTTAATTTTTGGCTTTAAAAAATCATTTT
GCTAAGCCTGAGATGAAGGCGAAATCTCGAGAAAAAGCATTAAAAAGTAAT
AAATTCGGTTAAAAACGACTTTTTCTATCACAGAAAGTGTTCTCTGAGTGCTA
ACAACCTTCTTCTGTCCAAATTTTGACACAATTTCCCAATTATGCCGACTTAT
TACACCTTTTTCCGTCAATCTTCTAGTTTTTCCCACCCTCTTGACCCCTGGTG
ACGTCATTTGTTTGTTCTTCTTCCAAGACATGCCCTGTGGGGTATTTTTTCTC
AAAATTTTTGCAAATTTATTGGATTCTAAATAAAATTCAGGAGTCTAGCACC
AGGAATAATAATGCAAATTTGAAAAAAAATTAACAGAAATAATGATTTTAA
ATGATTATTTAAATTTTAAATTTTAAATTTCCAGGAAAAACACCTGCAAGAAG
CGATTGGTGGCGAGGAAGGCGAGTAGATCGGGTATTCAGGTGAAGCATGTCA
TTCCAACCTCAAAAAGTCGACCGAGTCGAAGATCAACGCTATCACTCCACTTA
TCACAACAAGAATAAAATGCACCGTTCAAAGTATATCAAAGTTCATGGTGAG
TTTTTTAACCAAAATTCGGCGAAATAATTTAATTTCCGGTTTTTTGAAATT

34/92
FIGURE 16

AATTTCCGCTTGGGTTTTCTTGATTTATTATTTTTGAAATTCCTCTCTGAAT
TCGAAAGAAAATAACTTGATTTTTAGACTTCCGGCTAAAACCTTCAAAAAT
GTTTGTTGATTGGTTCCAAATTTTCGCCTGATTCCGAATTTCCGATGTGACAAA
TTCAAAAAAAATTCCTGATTTTATATTCAAGCTTTGTGTTTGTGTGTTCTTT
TTGGAGCGCGCTTGCATCGTTTGATTTTCTTCGTCTTTTTTAAATTTATTTTC
GCTTGTTTCATTCATTTTTGTGAGTTTTTTTTCTGCCAAAATGAATGAACTG
GTTTAAAAAATTGAATTCGGCGAAAATAAATTTGAAAAACGAAACAAATCAA
ACGATGCAAGCGCGCTCCAATGCGATTTTTTTGGGCGCGGAAATTCGTGAT
TTCAAGCTTAAATATAAAATCAGGTATATTTTTTCGACTTTTTTCACGTTGAAA
TTCGGAATCAGAGGAAAATTTTGAGTCAATCAAAAATATTTCCCAGATTTTCG
GTATCTTTAATGCATCAAAAATGAACTTTCACCCCCATACTCCCAGAAAAATA
AGAAAACAAATTGCGAATATTGTTCCCTGATCAAATTTTTCTTTTTTAACT
ACACTTCTCTGTTTTGAAGTGAGAAAGTACATTTTTCTGCGTTTCTTATCAGT
TATCATTTGAAAAGGATCAGAATTTGATGACGATATATTTGTTTAGTTACCTC
CCTTTTTCTGAACAGTTTTTGCGAAAAAAGGAGAAAAACCGGAATTTCTAT
GAAAATGTGATTTATTTTCAGCCTGGCAAGCACTCGAACGAGACGAACCCG
AGTATGACTACGACACAGAAGATGAAGCATGGCTATCAGATCACACTCACAT
TGACCCGCGCGTTTTGGAAAAGATATTCGACACAGTGGAGAGCCATTTCATC
GGAGACACAGATCGCGAGCGAAGATTGGGTGATTAATTTGCATAAATGTAA
GTTGACGAAATTTCCATTGAAACCCCCCCCCCAAAAATATCGTTTAATTG
CAGCACTGGACTCATCAATCGTGTACGAAATATACGAATATTGGCTGTGAA
GCGAACATCGGCTGCGACGACGTCTGGTTGTGTTGGAGTCGGTGGATTAAT
TCCGAGAGTCAGGACAGAATGTGGAAGGTAAGAATTTGACTATTTTGAAC
GAATTTCTGTGATGAACTTCTCTAAAACCTTTTAAAGTTTTTTATGGCGGTTCA
AAATTTCGGAAAATTTACACTGATTTTAGCTAAAACCTTGAATTTTGGTCATTT
GTCCGTGTACATCTGTCCGAAATCGACTTTTTTTGGAATTATCATCCTTTAT
TGCACATTTGGCTAGTTTATCTCATTTAATTTGTTGATTACTAAGGTACATTT
AAAGCCAATAGGTAACCAACCAAAAACCTATCATAATTTTTCTACACTTTTTAA
TTTTCCGACACTACTTGAATAACCCCATAGTGACCAATTTTGATAGTTTTTG
GCTGGTTACCGGCTTTAAATGTACCTTATTAATCAACAAAATTAATGAGATA
AACTAGCCAAATGTGCAATAAAGGATGATAATTCCATAAAAAGTCGATTTTG
GACAGATGTGACACGGGCAAATGACCAAAATTCAGTTTTTAGCTAAAATCA
GTGTATTTGTTTCGAAGTTTTGAACCGCTATAAAAAAATTTTTGGAATGCTTT
TGGAAGTTTCATTACGAAATTCATCTATTTCTATACGCAAAAATTAGAATT
TTCAATTAATAAATTCATTTTACAGGATGGACAAGGTGTTATCAATCCGTACGT
TGCATTCGTGACGTGCCGAGAAAATGCAGACTCGAAAGAATCGGAAAAA
CGATGAAGATTCGTATGAGAAGATTCTCAAGTTGGTACATGACATGTCGAAA
GCTCAACAGCTCTTCGATATGACTGCCCCGACGAGAAAAGCAGAAGCTCGCG
TTGATTGATATGGAATCGGAGATTTTAGCGAAACGAATGGAGATGTCAGATT
TTGGTGGTTCTCCGAGTTCGTTCAATGAGATCACCGAAAAGATTTCGAGCAG
CAGCAACGTTGGAAGTCGTGAAACCACCACTGGCAGAAATCAACGGATCAG
ATGAAGTGAAGAAGAGGAAGAAGCCGAGACGAAAGATTGCTGATAAGGATT
TAATATCGAAAGCCTGGCTTAAAAAGAATGCAGAAAGTTGGAATCGGCCCGC
CGTCGCTCTTTGGACAACACAGTGGAAATGTTCCGACGGTTACAACGAAGC
CAGTTCGAGAGTCGTTGGCGAATGGGCGATTTGCGTTCAAGCGGAGGAGA
GGATGTGTTTATCGCGCGGCTCTCACC GTTTACAATGTGCCTACAGCGCCT

35/92
FIGURE 16

GCTACAGTACCTCCAGTACAGACTCAAGCAGCAGTGGCTTCATCATCATCG
TCAAAATCAACGGATATGGTGCCGTGGAACATGAAGTTCTTTGAACTTTTG
TTCGGGATTACAGGATTAGTTCTCGATCTCTTGGCTTTGTACGCCGACG
AATGGGACGAGGTGGGCGAGTTGTATTGATCGGATGCCTCGCAATCGAG
ACGACAACGACGAACGCACTTCGACAGATCCATGGGCCGAGTATTGTGTG
CGGATAGTTCAAGGTGAGATTTTTGAATAAGAATCTTAATTTACAGAGATTT
GGTTTTTTTCGCTGCTTTTTCTGTAATTTTGTGGTATTTTTCTCGTATTTTCA
ATTA AAAAACGGGTTTTAAATAATTTTAACTGAAATTTGCTAAAAACCAAG
AAATTTTATTAAAAAATGCAACAAAAAAGACTGGAGGCACCACCGAATG
GAGAACAGGAGAACCCAAAACACGCCCATTTTTCCGTGCCGGGCGGCGA
AAATTTTTGCAGAATTTGCTGCAATTTTTCGTTTTACAAACGAAACAACGAAG
CTCTGAATGTGTTATTTGGAGCTTCGTTGTTTCGTTGTAAACGAAAAATT
GCAGCAATTTCTGCAAAAATTTGCGCGCGGCACGGAAAAATGGGCGTAGTT
TTAGGTTCTCCTGTTCTCCTTTCCGGTGGTGCCTCGAGTCTTTTTCGCATTCT
AATGAAATTTCTTTGTTTTTAGCGAAATTTAGGTTAAAATTATTTAAACCC
GTTTTTTTTTCAATTGGAAATGCGAGGAAAAACCACAAAATCACAGAGAAAG
CTTTTGGATTTTTTCGCAGCTTTTTCTGTGATTTTGTGGTTTTCTCGCATTT
TCAATTGAAAAAAAACGGGTTTTAAATAATTTTCACTGAAATTTGCTAAA
AACGAGGAAATTTATTACAAATGCAAAAAGACTGGAGGCACCACCGAAA
CCGAATGCAGCTCAGAACAGGATTTACCAAAACAGGATGCAGTAGGCGGAG
CCAATTCGCAACCACCGCATGCTTATTTTCGCATGCCTCGCACGTTTTTTTT
CTCTTGAAACAATGCAACAATATCAAGGAAAAAACGTGCGAGACTTGCGAAA
TAAGCATGCGGTGGTTGCGAATTGGCTCCGCCCACTGCATTCTGTTTTGT
AAATTCTGTTCTGAGCTGCATTCTGTTTTGTTGGGGCTTCCAGTCTTTTTGT
GCATTTTAAATGGAATTTCTTCGTTTTTAGCGAAATTTAGGTTAAAATTATTT
AAAACCCGTTTTTTTTTCAATTGGAAATGCGAGGAAAAACCACAAAATCACA
GAGATAGCGAGGCCCCACGAAAAGGGGAGCAGAACAAAAAGGGGGGGG
GGGGGCTGGCACTGTGCCAAACGCACAAAACGCTTTTTATTCTTATTCAACG
CACGACTTTGTTATAACCACTCCGTTATTACGCATCGCGCGCTGTTAGC
GTGAAAATACAAAAAACGTCGTGCGTTGAATGAGAATAAAAAAGCGTTTTG
TGCGTTTGGCACAGTGCCAGCTCTCCTTTTCGCAGATCCCCTTTTCGTGGG
GCCTCAGAGAAAGCTGCCATAAACTTTTTCTTCGCGCTAAGACCAATACCA
ATAAATCCTTGCGCCTTTAATATGCAAACTATATTTTTCTTCCAGAACCTTCC
GTGCTCGAAACAGTTGCTTGGTACCGAAGAAGAAACCGATGATCTAAGCC
CGAAATCTCTGTATTTGCTCGCAGTAATCGGTTTCGCATTCAACGATGATGA
AACTGAACGGGAATGGACTTCAAGATGCCAACAATCATCGTGGAGAGATAC
AGAGGTGGATGATGAGCTGAAAAAGCGGGAAACAACGTCTGAAAGTGAGAT
TTTGAACGATTTACCTGGGAAAATAGATTATTTTGGGCCTATTTAATTATTTA
ATTGCAGAATTTACCGAAACCACGACGAATGGAAGTACCAAAACACACACA
GAATCGGATGATAGTGAAGTTGAACGGATGGAGGTTGATGATCAAGTTGAT
GAAGCTCAAATAACTGTATCATCATCAAAGACGATGGAATGAATGGAATG
ATAAGAACGAGGATGAAGAAGATGATGATGATGATATGGATGTAGATGAACA
TCAGAGTGTGCTGGGTGTGGATCAGCAGGAGGAGGAGGAGCATCACCAGC
AAAAAGTTCCGGCATCAAATGAATGGTGGTGGTGGTGGTGGTGGAGTGGTAA
AACTGAAACCGCCGCTGCAAGAACTTTCCGCCCGCTTTCGGGAAACGGAA
GAGCGGACAGAGCGGAACCGACGCCGTTCCGGCAAAGGTAGTGAGGCTT

FIGURE 16

TTTTTTTAAATACTCGAAAAAGAAGGAAAAAATCCCACTTTTAAAAATACGAT
TCTTAAAAATGCGAATCCCTCCAAAATGAGAACTCTGATTGGCCAGGGAGC
TCTCATTTTGAATGGAAATTAGTCAAAATTGAAAAATCCCGTTTTTTTTTAAAG
TTGGATTTTTCATTTTCTCGCGATTTTTTCCGCGTTTCTGTGTCATTCTGAA
TTTAAACATTTAATAAAATTAATAATGTCTGGAATATTGACAAATTATGCTTCAAA
TTTTTTGCGCGGGAGTTCAAAAATAATTTGGCCCTTTTTATTTTTATTTTGCA
AAAATATATAAAAAATCATTTTAAAAAATTTAGAAACATTTTTTAATTTTTTAA
CAGTTATATTGCTATATTGGGACGGTATTCTGTCATTAAACTTGGTGTGTC
GAATTTTTTTTTATTGCTTTATAAGACTCAAAATTGTCTGAAAACACCGAATTTT
ATAATGAACTTCTTGGAACCTCTCAAAAAAAGTTATGACGGCTCAAAAAA
TGACCTAAAATTTGTTAAAATTTGAAATTTGACTTGTGCAACGGCTGGAAAC
AATTTTTTTTTTTGAAATCACCGTCAAATTTTGAATATAAAATTTAATTATTTTG
CGTTTTCAACTCGATTTTTGGTATTTTCAAGTCGATGGACGGCAAGATTTGG
TTAAAAAATTAAGCCGTCCATTTTCTCGCCGTCCATTGACTTTAAACTACC
TAAATCGAGTTGAAAACGCAAGATAATTGACATTTATACCCAAAATTTGACTG
TGTTTTTAAAAAAGTTAGTTTCCAGCCGCTGCGACAAGTCAAATTTCCAATTT
TAACTATTTTAGGCCATTTTTTGAAGCCATCATAACTTTTTTTTGAAGAATTTT
AAGAAGTTTCATCATGAAATTCGGTGTTTTCAAGACAATTTTGAATCTAATAAA
GTAATTTTAAAAAATTCGACAGACACCACCTTTATAGCAATTTTGAATTTTTTT
TTAAACTTGTCTTGAAAAATCTTGAAAAAAGTCGAATAAATTTCCCATTTTCT
ATTTTCTTTTTTGCAGATGTGCGGAACGGTGTGCGACTCAGATGATTGGAGA
GAGCCGAGTGGATCACCATCAGAATCGAATTCATCAACCGAATGGGGTGGC
TATACGCCACAAGAACAGCATGCAGTTGTTGTTGCCAACGCGGTAGCTGTC
GCTTTCAAGGAAAAATTGATGAATGGCGTGGATGATGATGATGATCAACAAC
CATCGCCGGCTAGAGGAGCACGAGATCATTCCATCAAAGAGTTCGTTAGTT
TTTCTTTGCTTTTTTTTTTTTTGATTTTTGAGAGCAAATTTGAAAAGTTTTACA
CGGTTTTTAAAAAATGTTGAAATTAATAATTTGTTGAGAATTTGATTTGAGC
AAGTTTTATTTTTAAAAAATTGAATTTTTTCAAGAAATTTCTGAGTTTTCTTTTTAA
AAAATTGAAATTTTCAAGAAATTTCTGAGTAGCAAGAATCTTTAAGATCCTTAA
TTTCTATGCAAGAATACGTAGGAGTTTTACTTTGCTCAGGAAATTTATTTTTT
GTCAGAGGAGTATATCCGAAAAAGAACAATAAATGCACATTTCTCAAAAC
GCGTATTTTTTTTTTCAAGTTGATGTCAACGGTAACACTGCTGGAACGGAAAA
AGTTCATGATGCCGTGCAATCGGTCTATTAATTTGAACTCTCTGCTGCTGC
TTCTGCTACTGCTGCTACTGCTGCTCATCGCCAATTTTCAATCCTCCTGAGA
TTTTTGTATGGTCATTCATTGTTTTGTGCATATCTCTCTCTCTCTCTCTCTC
CCATGATTTCTCAAATATTTCAATGTATTTACACCCCCACTCTGTCCGCTGCCT
AATCCCCGACCGAATAATCAGATTGCTGGAATAATCTGCGATTCTTTAATA
TTGCAACCAACCAACCAATAATATGTGTCTCATCATCTCGGTACTCTCACTT
GAGCCGTGTTTTCTGTAGTATTTTATTCTCTAAAAAATAATCATTTTTAATATA
ATATACGTACACATTTATATCTGTAATATATATTTTTTAAAAATGATCCCCCT
CCCTCCATTGTTGTTTTTTTTTCTGTGGGTTTCAAGCTTTTGAAGTGTGAAA
AATCTCATCCCATCATCATTTTCTATTGTTTTTTTTTCAAGTTGAAATATCTTA
TTTTATCTTTTTCTTTTTTTTTTCAATTTTTTTTTTTGATGGTGGGGATTGATT
TTTCTGTCGGCGAAACGCCCGCCGCCGCAATCCCACTCTCTCTCTCAGT
CTCTTCTTAATGATCTTCGAAACTATTTTTATTTCCCTCATTAACAATTACGAG
GTCGTCTTTTTTTTTTCCCCACCCCCCACTGTTTGGTGTAAATTTTGTGTTGCG

FIGURE 16

GGAGGTTTTTGTGTGTGGATTTTGGATTTTGGATTTTCAACAAAAA
TTCCCCCGAAATCAAATTTTTCCCATTTCCCCTCAATATTAGTACTGTTG
TATAAATAAACTTGCTCTCTCTCTCTCTCGAAATCTCCTACTATTATTTTT
TAAAAGATTTTCCAACAAAAATTCAAAAAACACACAAACGACCTCTCTGCA
CGCGGTAATCCTCTCTCTTTTGTCCCCCATTTTCTCTGTTTCTCTTTTTTCT
ATCCCCTATACCTGTGATTGGAATATC

FIGURE 17

epc-1 ORF

ATGCCCACTACTTCGAAGGCGTTTCGAGCCCGGGCGCTCGACTCGAACCG
GTCTATGACTGTATACTGGGGCCACGAACCTCCGGACCTATCAGAATGCAG
TGTTGGAAACCGGGCGGTGACACAAATGCCGTCTGGCATGGAAAAAGAAGA
AGAACAGGAAAAACACCTGCAAGAAGCGATTGCTGCCCAGCAAGCCAGTAC
ATCGGGTATTGAGCTGAACCATGTCATTCCAACCTCCAAAAGTCGACCGAGTC
GAAGATCAACGCTATCACTCCACTTATCACAACAAGAATAAAATGCACCGTT
CAAAGTATATCAAAGTTCATGCCTGGCAAGCACTCGAACGAGACGAACCCG
AGTATGACTACGACACAGAAGATGAAGCATGGCTATCAGATCACACTCACAT
TGACCCGCGCGTTTTGGAAAAGATATTGACACAGTGGAGAGCCATTATC
GGAGACACAGATCGCGAGCGAAGATTGCGTGATTAATTTGCATAAATCACT
GGACTCATCAATCGTGTACGAAATATACGAATATTGGCTGTGGAAGCGAACA
TCGGCTGCGACGACGTCTGTTGTGTTGGAGTCGGTGGATTAATTCCGAGA
GTCAGGACAGAATGTCGGAAGGATGGACAAGGTGTTATCAATCCGTACGTT
GCATTCCGTGCGACGTGCCGAGAAAATGCAGACTCGAAAGAATCGGAAAAAC
GATGAAGATTGCTATGAGAAGATTCTCAAGTTGGTACATGACATGTCGAAAG
CTCAACAGCTCTTCGATATGACTGCCCGACGAGAAAAGCAGAAGCTCGCGT
TGATTGATATGGAATCGGAGATTTTAGCGAAACGAATGGAGATGTCAGATT
TGGTGGTTCTCCGAGTTCGTTCAATGAGATCACCGAAAAGATTGAGCAGC
AGCAACGTTGGAAGTCGTGAAACCACCACTGGCAGAAATCAACGGATCAGA
TGAAGTGAAGAAGAGGAAGAAGCCGAGACGAAAGATTGCTGATAAGGATTT
AATATCGAAAGCCTGGCTTAAAAAGAATGCAGAAAGTTGGAATCGGCCGCC
GTCGCTCTTTGGACAACACAGTGGAAATGTTCCGACGGTTACAACGAAGCC
AGTTCGAGAGTCGTTGGCGAATGGGCGATTTGCGTTCAAGCGGAGGAGAG
GATGTGTTTATCGCGCGGCTCTCACCGTTTACAATGTGCCTACAGCGCCTG
CTACAGTACCTCCAGTACAGACTCAAGCAGCAGTGGCTTCATCATCATCGTC
AAAATCAACGGATATGGTGCCGTGCAACATGAAGTTCTTTGAACTTTTGT
CGGGATTACAGGATTGAGTTTCTCGATCTCTTGGCTTTGTACGCCGACGAA
TGGGACGAGGTGGGCGAGTTGTATTGATCGGATGCCTCGCAATCGAGAC
GACAACGACGAACGCACTTCGACAGATCCATGGGCGGAGTATTGTGTCGCG
GATAGTTCAAGAACCTTCCGTGCTCGAAACAGTTCGCTTGGTACCGAAGAA
GAAACCGATGATGTAAGCCCGAAATCTCTGTATTTGCTCGCAGTAATCGGT
TCGCATTCAACGATGATGAAACTGAACGGGAATGGACTTCAAGATGCCAAC
AATCATCGTGGAGAGATACAGAGGTGGATGATGAGCTGAAAAAGCGGGAAA
CAACGTCTGAAAAATTTACCGAAACCACGACGAATGGAAGTACCAAAACACA
CACAGAATCGGATGATAGTGAAGTTGAACGGATGGAGGTTGATGATCAAGT
TGATGAAGCTCAAATAACTGTATCATCATCAAAGACGATGGAATGAATGGA
AATGATAAGAACGAGGATGAAGAAGATGATGATGATGATATGGATGTAGATG
AACATCAGACTGTCGTGGGTGTGCATCAGCACCAGCAGCAGCAGCATCACC
AGCAAAAAGTTCGGCATCAAATGAATGGTGGTGGTGGTGGTGGTGGAGTG
GTAAAACGAAACCGCCGCTGCAAGAACCTTTCGCCGCCGCTTTCCGGGAAAC
GGAAGAGCGGACAGAGCGGAACCGACGCCGGTTCGGGCAAAGATGTGCG
GAACGGTGTGCGGAGTCAGATGATTGGAGAGAGCCGAGTGGATCACCATCA
GAATCGAATTCATCAACCGAATGGGGTGGCTATACGCCACAAGAACAGCAT
GCAGTTGTTGTTGCCAACGCGGTAGCTGTGCTTTCAAGGAAAAATTGATG
AATGGCGTGGATGATGATGATGATCAACAACCATCGCCGGCTAGAGGAGCA

FIGURE 17

CGAGATCATTCCATCAAAGATTCGATGTCAACGGTAACACTGCTGGAACGG
AAAAAGTTCATGATGCCGTCGACAATCGGTCTATAA

FIGURE 18

EPC-1 protein

MATT SKAFRARALDSNRSMTVYWGHELPDLSECSVGNRAVTQMPSGMEKEE
EQEKHLQEAIQAQASTSGIQLNHVIPTPKVDRVEDQRYHSTYHNKNKMHRSK
YIKVHAWQALERDEPEYDYDTEDEAWLSDHTHIDPRVLEKIFDTVESHSSETQI
ASEDSVINLHKSLDSSIYIEIYEWLSKRTSAATTSGCVGVGGGLIPVRTECRKD
GQGVINPYVAFRRRAEKMQRKRNKNDSDSYEKILKLVHDMMSKAQQLFDMTAR
REKQKLALIDMESEILAKRMEMSDFGGSPSSFNEITEKIRAAATLEVVKPPLAEIN
GSDEVKKRKKPRRKIADKDLISKAWLKNAESWNRPPSLFGQHSGNVPTVTTK
PVRESLANGRFKRRRGCVYRAALTVYNVPTAPATVPPVQTQA AVASSSSSK
STD MVPSNMKFFETFVRDSQDSVSRSLGFVRRRMGRGGRVVFDRMPNRDD
NDERTSTDPWAEYCVADSSRTFRARNSSLGTEEETDDLSPKSLYFARNRFAF
NDDETEREWTSRCQQSSWRDTEVDDELKKRETTSEKFTETTTNGSTKHTES
DDSEVERMEVDDQVDEAQITVSSSKDDGMNGNDKNEDEEDDDDDMDVDEHQ
TVVG VHQHQQQQHHQKVRHQMNNGGGGGGGVVKLPPLQELSPPLSGNGR
ADRAEPTPVPKMCMTVSDSDDWREPSGSPSESNSSTEWGGYTPQEQHAVV
VANAVAVAFKELMNGVDDDDDDQQPSPARGARDHSIKDSMSTVTLLERKKFM
MPSTIGL

FIGURE 19

ssl-1 Genomic

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cagctgatgt tgttgatgga aaaatgacgg ctgcaaagaa gccattggct gcaactgagc 60
caaaagtgca taataaataa atgtgtttct aggatcttct aataattttt tttctgtttt 120
ctagctctaa acttgatatt atttcattct tgttctacca aattcccacg gattctacgc 180
tttatgtttc taaattatta ttctttttta tttatatctg cattttcttc taaaaactct 240
ggtcattttc ttgttttttt cttggttaatt ataaaaatta gtcatacaaa tcttgttaaa 300
tatctggcta ttcagtgaac aaaccatttt ccgctctaaa ttcgaccgca atcaatcgaa 360
aaatggctca aaacgatgcc atctggctgc aacccccctg tcgtctctca attttggtgta 420
ctctctcgca gccacgcacg cgacgcaacg cactcgcgtc gcggtcgagc ttctttttca 480
aatttatcgc gccatttttg ttttgcttca tatttatcgg ctcacgattg attttcgtcg 540
aaaaacgcgc ttaatcgatt cctttttacc tgaaaaatgt tgttccaatt ggaaaaccag 600
ttgaagatcg atgaattttc aagaaaatca ttcaaatagg caaaaccgcg tgaactttga 660
aattcgattt ttgagttttt tgaagaaaat ataattattt catcatttat gttggtcctg 720
ttggtcctca gcatagaaaa ttcggacatg acattagaaa ttcataataa ctgctcccaa 780
tatcgggatt agaacgattt tcagctcaaa atatggaaaa ttggttacat aaaccgcata 840
ttttagcat taatcttgaa cagctatatg gcattaaaaa aaaatatata tatacattgt 900
ttttctctc gaagtttctc tttttgttct taaaatccgg aatataattt aaaaaaccac 960
ataaatttca atttgcagta cgagttcccc ccgaatcaca atg ccg gca aca ccg 1015
                               Met Pro Ala Thr Pro
                               1           5

gtg cgt gct tca agt act cga ata agc aga cgt aca tca tca aga tca 1063
Val Arg Ala Ser Ser Thr Arg Ile Ser Arg Arg Thr Ser Ser Arg Ser
                10                15                20

gtg gct gat gat cag cca tca act tcg tct gcg gtg gct cca cct cct 1111
Val Ala Asp Asp Gln Pro Ser Thr Ser Ser Ala Val Ala Pro Pro Pro
                25                30                35

tca ccc att gcc ata gaa act gat gaa gat gcg gta gtt gag gag gag 1159
Ser Pro Ile Ala Ile Glu Thr Asp Glu Asp Ala Val Val Glu Glu Glu
                40                45                50

aaa aag aag aaa aag aca tca gat gat ttg gaa att atc act cca aga 1207
Lys Lys Lys Lys Lys Thr Ser Asp Asp Leu Glu Ile Ile Thr Pro Arg
                55                60                65

act cca gtc gat cgg cga att ccc tac att tgc tcg att ctt ttg act 1255
Thr Pro Val Asp Arg Arg Ile Pro Tyr Ile Cys Ser Ile Leu Leu Thr
                70                75                80                85

gaa aat cga tcg att cgc gat aaa tt gtacgatttt ttaaatttaa 1301
Glu Asn Arg Ser Ile Arg Asp Lys Leu
                90

ttactttcct caaatccgaa taattattag atcgcgcttc gcgtttctgc atccgcggta 1361
ttttgccttc ccactgaaaa tagcagattt atcgaatttt tagcttaaaa aaaaaatggt 1421
ttttctgcat ttttcaaaca aaccttttgt aaaacagtga aaatcgaatt tcaaatgact 1481
aaaatgaatt ttttttttgt ccaactggtg tggaatgggt tgaatttgaa gaaatcagcg 1541
ggatttttcg tattttctga atatttttct attaaaaatc ggtttcaaac cattttttga 1601
cttttgaata gaaaaatatt gagaaaaatc gaaaaatcca gctaacttcc agcttggtca 1661
aattcaaac attccacaac cagtggacga aaaaagttca ttttagtcat ttgaaattcg 1721
atttggttg tttgaaaaat gcaaaaaaaaa aatatttttt aaagctaaaa atttgataaa 1781
tctgaaaaaa atctgctatt ttcagtggaa aggcaaaata ccgcgaagcg cagcaagcgc 1841

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FIGURE 19

gctctaataa	ttattccgct	tcgagaagag	cgtgtattat	ttcattgtta	catttcataaa	1901
ttatgaatta	atgtttttca	g g gtt	ctg agc	agc ggt	cca gtt	cgt caa gaa 1953
			Val Leu	Ser Ser	Gly Pro	Val Arg Gln Glu
		95			100	
gat cac	gaa gaa	cag att	gct cga	gct caa	cgg ata	cag cca gtt gtc 2001
Asp His	Glu Glu	Gln Ile	Ala Arg	Ala Gln	Arg Ile	Gln Pro Val Val
105		110			115	120
gat caa	att caa	cga gtc	gag caa	at gtatgtgaag	ctgaaaaatt	2047
Asp Gln	Ile Gln	Arg Val	Glu Gln	Ile		
		125				
gcaccacaaa	tcaattattc	taattctgtt	ttacag c	ata ctc	aat ggt	tca gtg 2102
				Ile Leu	Asn Gly	Ser Val
				130		135
gaa gat	att ctg	aaa gat	cct cga	ttc gca	gta atg	gca gat ctc aca 2150
Glu Asp	Ile Leu	Lys Asp	Pro Arg	Phe Ala	Val Met	Ala Asp Leu Thr
		140		145		150
aaa gaa	cca cca	cca aca	cct gca	cct cct	cct cca	atc cag aag aca 2198
Lys Glu	Pro Pro	Pro Thr	Pro Ala	Pro Pro	Pro Pro	Ile Gln Lys Thr
		155		160		165
atg caa	ccg att	gag gtg	aaa att	gag gat	tca gag	ggc tca aat acg 2246
Met Gln	Pro Ile	Glu Val	Lys Ile	Glu Asp	Ser Ser	Glu Gly Ser Asn Thr
		170		175		180
gct caa	ccg agt	gtt ctg	ccc agt	tgt gga	gga gga	gag acg aat gtg 2294
Ala Gln	Pro Ser	Val Leu	Pro Ser	Cys Gly	Gly Gly	Gly Glu Thr Asn Val
		185		190		195
gaa aga	gcc gcc	aaa aga	gtgagttttg	aagatagatt	gggtgtgtaaa	2342
Glu Arg	Ala Ala	Lys Arg				
200		205				
aaatgaatgt	ttatatattc	actgcaactt	tttctctcacg	agggacgagg	aaaagtggtt	2402
tctaggccat	ggccgaggtg	ccgacaagtt	tcagcggcca	tttatcttgc	tttgttttcc	2462
gcctgttttc	tttcgttttt	catcgatttt	tttcgttttt	tcttaataaa	actgataaat	2522
aaatattttt	tgcagatgct	aaaacaattt	ccaagtaaaa	aaattatgta	ttcagtgggc	2582
aagcagcggt	gaaagtggtc	aatgcaatat	gatggattac	gggaatacaa	aacctaaact	2642
ttttctgaaa	catgatacat	acgctgctta	aatgctgaga	ctacctgatt	ttcataacga	2702
gaccgctgaa	aaagttttga	ggttttcaaa	attcaaattt	tttggtgaaa	aagtcgagat	2762
tttcgcacaa	aaagttgaat	tctgaaaacc	tcaaattttt	ttcagcggtc	tcgttatgaa	2822
aatcaggtaa	tttcagcatc	atatgtatca	tgtttcaaaa	aaagtttagg	ttttgtattc	2882
ccgtaatcca	tcatattgca	ttgaccactt	tcaccgctgc	ttgcccactg	aatacatgat	2942
tttttacttg	gaaattgttt	tagcatctgc	aaaaaatatt	tatttatcag	ttttattaag	3002
aaaaaacgaa	aaaaatcggt	gaaaaaacgaa	agaaaacagg	cggaaaacaa	agcaagataa	3062
atggccgctg	aaacttgctg	gcccctcggc	catggcctag	aaaccacttt	tcctcgtecc	3122
tcgtgaggaa	aaagttgcag	tgttattgta	aatctcacaa	gagtcctggca	tgattttctca	3182
aaggcgcatg	gatttattca	gccctaaaat	taaataaatc	catacgactt	taaaggtgga	3242
gttcggaaaa	tgaggatttt	actttaaaaa	gtcctaaacta	gtcccaaatg	ccgaattacc	3302
acaaaagaaa	aacggaaaaa	aattcatcaa	gtttgaaaaa	aatgcggatg	attttgttga	3362
aatttcaacg	ctcgctaata	ttcctaattt	gaaccgcgct	tttgctccgc	ccgcactctg	3422
tagaattgca	tccgcctgtg	ttccttcctc	ttccggcgcc	ctacttcttt	tcgatttgaa	3482
atgatgaaaa	aatgagacaa	aactagaatt	cacgtagcgc	gtcggaaaatg	atgaaaatat	3542

FIGURE 19

catggatgca gcagatctac ggagtgcggc gcggacaaac ggcgcggtaa ttcaaagtga 3602
 gaatattagc gagagttgaa atttcaacaa aatcagccgc atttttttca aacttaattgt 3662
 attttttttc gtttttcttt ttagtaatt cggcatttgg ggctagtgtg agcattttta 3722
 agtaaaatcc tcattttccg aactccacct ttaaagggtg agtaccgaaa tttgagactt 3782
 tgctttttta ggcccaaatt ggtccaaaac taccgaattt tgtaatgaga cgttctgaaa 3842
 atttatccaa aaaatgttat ggcggttcaa agttcggcaa aataggggcc attttcagct 3902
 aaaatcaaat ttttttttcc aactttttcg gtgtcgcgcaac gtctggagcc taatttttat 3962
 ttattaatca ctttttaata aatattgtag cctttgatta ggcgtttatt cgctgattta 4022
 agtacattta tggtttttgg ggcacaaata aaagtttcat tttatgcccc aaaaaccata 4082
 aatgtactta aatcagcgaa taaacgccta atcaaaggct acaatattta ttaaagagtg 4142
 atgaataaat aaaaattagg ttccagacgt tgcgacaccg aaaaagttgg aaaaaatttt 4202
 gatttttagct gaaaatgtgc cttattttgc cgcgaacttt gaaccgcat aacttttttt 4262
 gagaaagaaa ttttcagaac gtctcattac gaaattcggg agtttttaaac caatttgggt 4322
 ctaaaaagtt tcaaattcca ataaaacata ccaaagcttt gtgaaattac aataaactat 4382
 tcctaaacgt attataatcc atttcaatt cttgcag gaa gcg cat gta ttg gct 4437

Glu Ala His Val Leu Ala

210

cga atc gcc gag ctc cgt aag aac ggc tta tgg tcg aac agt cgt ctg 4485
 Arg Ile Ala Glu Leu Arg Lys Asn Gly Leu Trp Ser Asn Ser Arg Leu
 215 220 225

cca aag tgc gtc gaa cct gaa cgt aat aaa acg cat tgg gat tat cta 4533
 Pro Lys Cys Val Glu Pro Glu Arg Asn Lys Thr His Trp Asp Tyr Leu
 230 235 240

ctg gaa gag gtc aaa tgg atg gca gtt gat ttc cga acc gag acg aat 4581
 Leu Glu Glu Val Lys Trp Met Ala Val Asp Phe Arg Thr Glu Thr Asn
 245 250 255

acg aag cga aaa atc gcc aaa gtt ata gct cac gcc att gcg aaa cag 4629
 Thr Lys Arg Lys Ile Ala Lys Val Ile Ala His Ala Ile Ala Lys Gln
 260 265 270 275

cac cgc gac aag cag atc gag att gag aga gcc gcc gaa cgg gag atc 4677
 His Arg Asp Lys Gln Ile Glu Ile Glu Arg Ala Ala Glu Arg Glu Ile
 280 285 290

aag gag aag cga aaa atg tgt gca gga atc gcg aag atg gta cgg gat 4725
 Lys Glu Lys Arg Lys Met Cys Ala Gly Ile Ala Lys Met Val Arg Asp
 295 300 305

ttc tgg tcg tct acg gat aaa gtt gtg gat att cga gcg aag gaa gtt 4773
 Phe Trp Ser Ser Thr Asp Lys Val Val Asp Ile Arg Ala Lys Glu Val
 310 315 320

ctg gag tcg agg ctc agg aag gcg aga aat aag cat ttg atg ttt gta 4821
 Leu Glu Ser Arg Leu Arg Lys Ala Arg Asn Lys His Leu Met Phe Val
 325 330 335

att gga caa gtc gat gaa atg agc aat att gtg caa gaa gga ctt gtt 4869
 Ile Gly Gln Val Asp Glu Met Ser Asn Ile Val Gln Glu Gly Leu Val
 340 345 350 355

tca tcg tcg aaa tcc cca tca att gca tcg gat cga gat gat aaa gat 4917
 Ser Ser Ser Lys Ser Pro Ser Ile Ala Ser Asp Arg Asp Asp Lys Asp
 360 365 370

44/92

FIGURE 19

gaa gaa ttc aaa gca cct ggc tct gat tca gaa tct gac gat gag cag 4965
 Glu Glu Phe Lys Ala Pro Gly Ser Asp Ser Glu Ser Asp Asp Glu Gln
 375 380 385

aca att gca aac gcg gaa aag tca cag aaa aag gaa gat gtt cga cag 5013
 Thr Ile Ala Asn Ala Glu Lys Ser Gln Lys Lys Glu Asp Val Arg Gln
 390 395 400

gaa gtt gat gct ctt caa aac gag gca act gtg gat atg gat gac ttt 5061
 Glu Val Asp Ala Leu Gln Asn Glu Ala Thr Val Asp Met Asp Asp Phe
 405 410 415

ttg tac act tta ccg ccg gaa tat ctg aag gct tat ggt ctg acg cag 5109
 Leu Tyr Thr Leu Pro Pro Glu Tyr Leu Lys Ala Tyr Gly Leu Thr Gln
 420 425 430 435

gag gat ttg gag gag atg aag cgc gag aaa ttg gag gag cag aag gct 5157
 Glu Asp Leu Glu Glu Met Lys Arg Glu Lys Leu Glu Glu Gln Lys Ala
 440 445 450

cgg aag gaa gct tgt ggt gat aat gag gag aaa atg gag att gat gaa 5205
 Arg Lys Glu Ala Cys Gly Asp Asn Glu Glu Lys Met Glu Ile Asp Glu
 455 460 465

gtctcgtagga tgctcctaaa aaaattacct aaaaaaaatc gattttccct ggaaaaaatc 5265
 ctctggaaat gaccgaaaac gtcattggcg ctcgaaattt tgaaaaaaa aaccccccaa 5325
 atttccagct aaaatctcaa attttattgc atattttggt agttcttttg ttgtccgagg 5385
 tgcgtttttc agctgaaaaat gtacctgaat ctgcaagtaa acgaccaata tatgcaataa 5445
 atgatgataa ttaattttccg atactgaaat gtgggcgaaa ttgagattt cgactgaaaa 5505
 cgtcttaaaa atcacccaaa acccggttt accgcacgaa ggtttgaaga aaatggccaa 5565
 tttttagcca aaatctcaaa ttctgtccac ttttcagtca gaaattagtt ttttgaaatt 5625
 aattaacacc ttttattgca ttttttcgt gttttattcgt tgatcgagggt gctttttcgg 5685
 tcgatgggtg cacaaattcg gtaattgtgc atccatcggc tgaaaatgct ccagaatttg 5745
 cgaatgaacg gtgaaaattt aagatttttag attgaaataa gccgtttttt agagaaaaat 5805
 ggtcgttttg agacattaaa ttcaatttaa atccctctt tattttcag agc cca tca 5863
 Ser Pro Ser
 470

tca gat gct caa aag cct tcc acc tca agc tca gat ctc acc gcc gag 5911
 Ser Asp Ala Gln Lys Pro Ser Thr Ser Ser Ser Asp Leu Thr Ala Glu
 475 480 485

cag ctt caa gat cca aca gct gaa gac ggc aac ggt gat ggt cat ggt 5959
 Gln Leu Gln Asp Pro Thr Ala Glu Asp Gly Asn Gly Asp Gly His Gly
 490 495 500

gta ctt gaa aac gtg gat tac gtg aag ctc aac agt cag gat agt gat 6007
 Val Leu Glu Asn Val Asp Tyr Val Lys Leu Asn Ser Gln Asp Ser Asp
 505 510 515

gaa cga caa caa gag ttg gcg aat atc gca gaa gaa gcg ctg aaa ttc 6055
 Glu Arg Gln Gln Glu Leu Ala Asn Ile Ala Glu Glu Ala Leu Lys Phe
 520 525 530

cag cca aaa gga tat aca ctt gag acg aca caa gtc aag acg ccc gta 6103
 Gln Pro Lys Gly Tyr Thr Leu Glu Thr Thr Gln Val Lys Thr Pro Val

45/92

FIGURE 19

535	540	545	550	
cca ttc ctg att cga gga caa ctg aga gaa tat caa atg gtt gga ttg				6151
Pro Phe Leu Ile Arg Gly Gln Leu Arg Glu Tyr Gln Met Val Gly Leu				
	555	560	565	
gat tgg atg gtt aca ctt tat gag aag aat ttg aat gga att ctt gcc				6199
Asp Trp Met Val Thr Leu Tyr Glu Lys Asn Leu Asn Gly Ile Leu Ala				
	570	575	580	
gac gag atg ggc ctg gga aag acg att caa acg att tcc ctg ctg gct				6247
Asp Glu Met Gly Leu Gly Lys Thr Ile Gln Thr Ile Ser Leu Leu Ala				
	585	590	595	
cat atg gct tgt agt gaa tcg att tgg gga cca cac ttg att gtt gtg				6295
His Met Ala Cys Ser Glu Ser Ile Trp Gly Pro His Leu Ile Val Val				
	600	605	610	
ccg acg tct gtc att ctg aat tgg gag atg gag ttc aag aaa tgg tgt				6343
Pro Thr Ser Val Ile Leu Asn Trp Glu Met Glu Phe Lys Lys Trp Cys				
	615	620	625	630
ccg gct ctg aag att ttg acg tat ttt ggt acg gcg aag gag cgt gcc				6391
Pro Ala Leu Lys Ile Leu Thr Tyr Phe Gly Thr Ala Lys Glu Arg Ala				
	635	640	645	
gag aag cgg aag gga tgg atg aag ccg aat tgt ttc cat gtg tgc atc				6439
Glu Lys Arg Lys Gly Trp Met Lys Pro Asn Cys Phe His Val Cys Ile				
	650	655	660	
aca tca tac aag acg gtt act caa gat att aga gct ttt aag cag agg				6487
Thr Ser Tyr Lys Thr Val Thr Gln Asp Ile Arg Ala Phe Lys Gln Arg				
	665	670	675	
gtgcgtagaa attttgaaga tttgcggcga atttggcgaa tttgcataat ttttttaaaa				6547
ccaattttac cgataattgc gaaatttttc aatttttatac agtggtcgga aattgctata				6607
attagtataa tttttgcaaa aatttggtact tttttcgaaa ttttgaacca ccataaaaca				6667
tttttgaaca atttttaaga ggtttaataa cgaaattcgt tcatttgaac acattttggc				6727
gatatgaatc gcccgaaaaat gtccccaat agacctaatt tcttaacaaa aatttaaaaa				6787
aaaatggccc aaaattgtct caaaatttcg aaaaaaaaac cgtaatttca gctgaaatct				6847
caaaatttgc caaattttcc gtctcacgga gatcagaaaa agttttttgc atttttttgt				6907
ggtttatttt agcgttattt cgttaattta gatacatttt agcccaattt ttgcaaaaaat				6967
tataactaatt atagcaattt ctgacccctg acaaactttg aaattatcgg taaacttgg				7027
ataaatgggt tttttccaaa tttttaaaag gatattaaag gtggagtacc acaatttgag				7087
gctttgtttt tttttttgga cccaaattgg tccaaaacta ccgaatttcg taatgagacg				7147
ctctgaaaat ttctttctca aaaaaaaagt tacggcggtt caaagttcgc ggcaaaataa				7207
ggcccathtt cagctaaaaat caaaattttt tcccaacttc tcggtgtctc aacgcctgga				7267
acctaatttt tatatttca tcacttttta ataaatattg tgggtcttga ttgggctttt				7327
attcgttgat ttaagtacat ttatggtcag tggggcacaa aatgtaactt tttttcccaa				7387
agaccataaa tgtactttta tcaacgaata aacgccaat caaagaccac aatatttatt				7447
taaaagtaat gaataaataa taattagggt ccagacgttg cgacaccgag aagttggaaa				7507
atttttttat tttagctgaa taagggcctt attgtctcaa actttgaacc gccataaact				7567
ttttttgaga acgtctcgtt acgaaattcg gtagtttttg accaatttgg gtctaaaaaa				7627
acaaagtctc aaattttctg ttagagattt tttaaaaatt gatatttttt ttttcag gcc				7687
				Ala

46/92

FIGURE 19

tgg cag tac cta att ctc gat gaa gct caa aat atc aaa aac tgg aag	7735
Trp Gln Tyr Leu Ile Leu Asp Glu Ala Gln Asn Ile Lys Asn Trp Lys	
680 685 690 695	
tcc caa cgt tgg cag gct ctt ctg aat gtc cgt gct cga cgt cgc ctt	7783
Ser Gln Arg Trp Gln Ala Leu Leu Asn Val Arg Ala Arg Arg Arg Leu	
700 705 710	
ctc ctg acc gga act cca ctt cag aac tct cta atg gaa ctg tgg tcg	7831
Leu Leu Thr Gly Thr Pro Leu Gln Asn Ser Leu Met Glu Leu Trp Ser	
715 720 725	
ttg atg cat ttt ttg atg cca aca ata ttc tca agt cat gat gat ttc	7879
Leu Met His Phe Leu Met Pro Thr Ile Phe Ser Ser His Asp Asp Phe	
730 735 740	
aag gat tgg ttc tcg aat ccg ttg aca ggg atg atg gaa gga aat atg	7927
Lys Asp Trp Phe Ser Asn Pro Leu Thr Gly Met Met Glu Gly Asn Met	
745 750 755	
gaa ttc aat gct cca cta atc gga cga ctt cac aaa gtg ctc cgt ccg	7975
Glu Phe Asn Ala Pro Leu Ile Gly Arg Leu His Lys Val Leu Arg Pro	
760 765 770 775	
ttt att ctg cgg cgg ctc aag aag gaa gtt gag aag cag ctg cca gag	8023
Phe Ile Leu Arg Arg Leu Lys Lys Glu Val Glu Lys Gln Leu Pro Glu	
780 785 790	
aag act gag cat att gtg aat tgt tcg ttg tca aag cgg cag aga tac	8071
Lys Thr Glu His Ile Val Asn Cys Ser Leu Ser Lys Arg Gln Arg Tyr	
795 800 805	
ctg tac gat gac ttt atg agt cgt aga tca aca aag gag aat cta aag	8119
Leu Tyr Asp Asp Phe Met Ser Arg Arg Ser Thr Lys Glu Asn Leu Lys	
810 815 820	
tct gga aat atg atg tcg gtg ctc aac att gtg atg caa ctc cga aaa	8167
Ser Gly Asn Met Met Ser Val Leu Asn Ile Val Met Gln Leu Arg Lys	
825 830 835	
tgt tgt aat cat ccg aat ctc ttc gag ccg cgg cca gtt gtt gct ccg	8215
Cys Cys Asn His Pro Asn Leu Phe Glu Pro Arg Pro Val Val Ala Pro	
840 845 850 855	
ttc gtc gtt gag aag ctt cag ctc gat gtt ccg gct cgt ctc ttt gaa	8263
Phe Val Val Glu Lys Leu Gln Leu Asp Val Pro Ala Arg Leu Phe Glu	
860 865 870	
att tcg cag caa gat ccc tcc tcc tcc tca gct agt caa att ccg gaa	8311
Ile Ser Gln Gln Asp Pro Ser Ser Ser Ser Ala Ser Gln Ile Pro Glu	
875 880 885	
att ttc aat tta tcc aaa atc ggc tat caa tct tcc gtt cga tct gca	8359
Ile Phe Asn Leu Ser Lys Ile Gly Tyr Gln Ser Ser Val Arg Ser Ala	
890 895 900	
aaa cca ctc atc gaa gag ctt gaa gca atg agc act tat ccg gag cca	8407

47/92

FIGURE 10

Lys Pro Leu Ile Glu Glu Leu Glu Ala Met Ser Thr Tyr Pro Glu Pro
 905 910 915

cga gca cca gaa gtt ggc gga ttt cgg ttc aat cgg acg gct ttt gtt 8455
 Arg Ala Pro Glu Val Gly Gly Phe Arg Phe Asn Arg Thr Ala Phe Val
 920 925 930 935

gca aag aat ccg cat acg gaa gag tcg gag gac gaa ggt gtt atg aga 8503
 Ala Lys Asn Pro His Thr Glu Glu Ser Glu Asp Glu Gly Val Met Arg
 940 945 950

agt cgt gtt ctg gtgaattttt aggaaaattg agaaaatgat ctaattgttg 8555
 Ser Arg Val Leu
 955

aatttttttaa agaatttatg ggccacaagc cgatttgccg gaaattttga tttttggcga 8615
 tttgccgaaa attttgattt ttggcgattt gccagaaatt ttgatttttg gcaattatcc 8675
 gatttgccgg aaattttgat ttttggcgat ttgccagaaa ttttgatttt tggcaattat 8735
 ccgatttgcc ggaaattttg aattttggca attttccgat ttgccggaaa ttttgatttt 8795
 tggcaatttg ccgaattgcc ggaaattttg atttttggca atttgccgaa ttgccggaaa 8855
 ttttgatttt tggggatttg ccggaaattt tgatttttgg caatttgcct atttgcgga 8915
 aattttgatt tttggcaatt tgccgatttg tcggaattt tgatttttgg caatttgcg 8975
 atttgcgga aattttgatt tttggcaatt ttccgatttg ccaaaaattt tgatttttgg 9035
 cgatttgccg atttgcgga aaaacatttt gtgagccaat tttctcgaaa tttgggcttc 9095
 aatattttca aattattcca aattttccac tgattccgaa tatctaagta aaaaaaatt 9155
 ccctgatttt atatttcagc ttaaaatcgc taattttcgc gtcagagacg acgtcatgtg 9215
 tcgatttact ggatttttaa tctttgtcgg atgctaattt ccgtttttca acgagtttcc 9275
 ttcatttcca tcggtttttg acgaagtttt ctttgaaaat atgttcttaa ggtcaattaa 9335
 acgttttatt atcaaaaaaa actagcaaaa ttggctttta aaacacattt tcacagaaaa 9395
 ctccgacaaa aaccgacgaa aatgaaggaa acccccgtt tgaaaacaga aattagcatc 9455
 tgataaagat taaaatcccg taaatcgaca catggcgtct ggcgctctct gcacgaaaag 9515
 tcgcgatttt aagctgacat acaaaaaaag agggatatat ttttttacga atttttcaca 9575
 tagatattcg aaatcagggg ggaaaatttg gagaaaattg agaaaatttc tcagatttcg 9635
 gattaaaaat attcaatttt tgttttctta tattaaaaaa aaattaactt ttataatttt 9695
 tcag cca aaa cca att aat gga aca gct caa cca ctt caa aat gga aat 9744
 Pro Lys Pro Ile Asn Gly Thr Ala Gln Pro Leu Gln Asn Gly Asn
 960 965 970

tca ata cca caa aat gct cca aat cgt cca caa act tca tgc att cgt 9792
 Ser Ile Pro Gln Asn Ala Pro Asn Arg Pro Gln Thr Ser Cys Ile Arg
 975 980 985

tca aaa acc gtc gta aat aca gtt cca ctg acc atc tcc acc gat cga 9840
 Ser Lys Thr Val Val Asn Thr Val Pro Leu Thr Ile Ser Thr Asp Arg
 990 995 1000

agt ggt ttt cat ttt aat atg gcc aat gtt gga aga ggt gtt gtt cgt 9888
 Ser Gly Phe His Phe Asn Met Ala Asn Val Gly Arg Gly Val Val Arg
 1005 1010 1015

ttg gat gat tca gca cgt atg agc cca ccg etc aaa cgt cag aag etc 9936
 Leu Asp Asp Ser Ala Arg Met Ser Pro Pro Leu Lys Arg Gln Lys Leu
 1020 1025 1030

acc gga act gca acg aat tgg agt gat tat gtt ccg cga cac gtt gtt 9984
 Thr Gly Thr Ala Thr Asn Trp Ser Asp Tyr Val Pro Arg His Val Val
 1035 1040 1045 1050

48/92

FIGURE 19

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gaa aag atg gaa gaa tcg aga aaa aac cag ctg gaa att gtt cga agg 10032
Glu Lys Met Glu Glu Ser Arg Lys Asn Gln Leu Glu Ile Val Arg Arg
                1055                1060                1065

cga ttt gag atg att cgt gct ccg att att cca ctg gaa atg gtt gcg 10080
Arg Phe Glu Met Ile Arg Ala Pro Ile Ile Pro Leu Glu Met Val Ala
                1070                1075                1080

ctg gtt cga gag gaa att att gca gaa ttt cca cgt ttg gct gtg gaa 10128
Leu Val Arg Glu Glu Ile Ile Ala Glu Phe Pro Arg Leu Ala Val Glu
                1085                1090                1095

gag gac gag gtt gtg cag gag agg ctt ttg gag tat tgc gag ttg ttg 10176
Glu Asp Glu Val Val Gln Glu Arg Leu Leu Glu Tyr Cys Glu Leu Leu
                1100                1105                1110

gtg caa aggtagaatt ttgaaaatta ttactttgct ttttttttaa ccaaaattgg 10232
Val Gln
1115

cccaaaacta ccgaatttcg taatgagaca ttctgaaagc ttctcaaaaa aaaagttttg 10292
gccgctcaaa gttcgggaaa ataaggccca ttttcagctg aaatcaaaat tttttccaac 10352
ttctcgggtg cgcaacgtct ggaactaaaa ttttgaaaaa cgagaaattt tccatttttt 10412
gcaagctgaa aaatcaaaagt ttttttttcc tcaaaattgg acaaacaaaa aaattttttt 10472
ttgaaaattg atcgaaaaaa ttcaaaattt ctataatttt tcgatttttt aaataaaaact 10532
ttcatcattt ttcttccaaa ttttagtttt tcgattttta cttttttcaa aaaaaaattt 10592
tttaatacga aaaaaattca atttttagct taattctttt ttagacccaa attggtccaa 10652
aactaccgaa tttcgtaatg agacgttctg aacatttctc aaaaaaaagt tatgacggtt 10712
caaagttcgg caaaataagg ccatttttca tataaaatca aatttttttt ctaacttctc 10772
ggtgtcacia cgtctggaac ttaattttta tttaattatt acttttcaat aaatattgtg 10832
gtcttttatt aggcgtttat ttgttgattt aagtacattt atggtcaagt ggggccc aaa 10892
taaaagttac attttgtgcc cacatgacca taaatgtact taaatcaacg aataaacgcc 10952
taatcaaagg ccacaattat tattaaaaag tgttgaaata ataaaaatta ggttccagac 11012
attgtgacac cgagaagtta aaaaaaattt tgaatttagc tgaaaatggg ccttattttg 11072
ctgaacttta aaccgctata actttttttt gagaaatttt cagaacgtct cattacgaaa 11132
ttcggtagtt ttggaccaat ttgggtctaa aaaagaatta gagctaaaat tgaattttct 11192
tcgtattaaa aatttttttt ttgaaaaaag taaaaatcga gaaaactaaa tttggaagaa 11252
aaatgatgaa aattttattt aaaaaatcga aaaattatag aaattttgat cgattttttc 11312
gatcaatttt caataaaaaa ttttttgttt gtccaatttt gagggaaaaa aaaactttga 11372
tttttcagct tacaaaaaat ggaaagtttc tcgttttcca attttttgat gtggattttt 11432
atgagaaaaa atatataatg tcacaaaaaa tagattatta tctaaaaatc gaaaaaatta 11492
aattttccag ttttcaggaa aaaaatcggt aagaaattgt ttttccatta aagggtggagt 11552
accgaatttt gagacgctgc ttttttagac ccaaaatggg ccaaaactac cgaatttcgt 11612
aatgtacgc tctgaaaaat tttcaaaaaa aaagtgtgga ccgctcaaag ttttgaaaaa 11672
atggcatatt tttagctaaa atctcaaaat ttggcaactt atcggtgtcg cagcggttgg 11732
aacttaattt ttatttaatt gtcattcatt aatgcatggt ttggcatttc attatgtggt 11792
atttcggtga ttgagatgct ttttgtgcct gcatcgacca aaaaaccatc tcaatcaacg 11852
aaataacaca taataaaatg ccaaaatagc cattaaagga tgataatcaa ataaaaatta 11912
agtttcaacc gctgcgacac cgctaagttg ccaaaatttg agattttagc taaaaatggt 11972
ccatttttct aaaactttga gcggtcacaa cttttttttt gagaaatttt cagagcgtct 12032
cattacgaaa attggttaggt tcggaaccaat ttgggtctaa aaaagcagcg tctcaaaatt 12092
cggtaattca cttttaaagt tttcaattta aagtataaat tatccaatca aaaattgacg 12152
aaaaaatttt ttaaaaaatt tttcttcgga aaaaaaattt aattttaatt tttgtt aga 12211
Arg

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49/92
FIGURE 19

ttc gga atg tac gtc gaa cca gtg ctg acc gat gct tgg cag tgt cgt	12259
Phe Gly Met Tyr Val Glu Pro Val Leu Thr Asp Ala Trp Gln Cys Arg	
1120 1125 1130	
cca tca tcg tct ggt ctt cca tca tat att cgc aac aat tta tca aat	12307
Pro Ser Ser Ser Gly Leu Pro Ser Tyr Ile Arg Asn Asn Leu Ser Asn	
1135 1140 1145	
atc gag ctg aat tct cgt tct ctt ctc ctc aac acc tcc act aat ttc	12355
Ile Glu Leu Asn Ser Arg Ser Leu Leu Leu Asn Thr Ser Thr Asn Phe	
1150 1155 1160 1165	
gat acc cga atg tcg atc tca cgt gct ctt caa ttc cca gaa ctc cgt	12403
Asp Thr Arg Met Ser Ile Ser Arg Ala Leu Gln Phe Pro Glu Leu Arg	
1170 1175 1180	
ctg atc gag tac gat tgt gga aag ctt cag acg ttg gct gtt ctg ctt	12451
Leu Ile Glu Tyr Asp Cys Gly Lys Leu Gln Thr Leu Ala Val Leu Leu	
1185 1190 1195	
cgt cag ttg tac ctg tac aag cac aga tgt ctg atc ttc acg caa atg	12499
Arg Gln Leu Tyr Leu Tyr Lys His Arg Cys Leu Ile Phe Thr Gln Met	
1200 1205 1210	
tca aag atg ctc gac gtt ctg cag acc ttc ctt tct cat cac ggt tat	12547
Ser Lys Met Leu Asp Val Leu Gln Thr Phe Leu Ser His His Gly Tyr	
1215 1220 1225	
cag tat ttc cgc ctc gac ggt acc act ggt gtc gaa caa aga cag gcg	12595
Gln Tyr Phe Arg Leu Asp Gly Thr Thr Gly Val Glu Gln Arg Gln Ala	
1230 1235 1240 1245	
atg atg gag cgg ttc aac gcg gat ccc aag gtg ttt tgc ttc att ctg	12643
Met Met Glu Arg Phe Asn Ala Asp Pro Lys Val Phe Cys Phe Ile Leu	
1250 1255 1260	
tcg acg aga tcc ggt ggt gtt gga gtc aat cta acc ggt gct gac act	12691
Ser Thr Arg Ser Gly Gly Val Gly Val Asn Leu Thr Gly Ala Asp Thr	
1265 1270 1275	
gtg atc ttc tac gat tcg gat tgg aat ccg acg atg gat gct cag gct	12739
Val Ile Phe Tyr Asp Ser Asp Trp Asn Pro Thr Met Asp Ala Gln Ala	
1280 1285 1290	
cag gat aga tgt cat cgt atc gga cag acg agg aat gtc tcg att tat	12787
Gln Asp Arg Cys His Arg Ile Gly Gln Thr Arg Asn Val Ser Ile Tyr	
1295 1300 1305	
cga ttg att tcc gag cga aca att gag gag aat att ctg aga aag gca	12835
Arg Leu Ile Ser Glu Arg Thr Ile Glu Glu Asn Ile Leu Arg Lys Ala	
1310 1315 1320 1325	
aca cag aag cgg cga ctt gga gag ttg gca att gac gag gct ggc ttc	12883
Thr Gln Lys Arg Arg Leu Gly Glu Leu Ala Ile Asp Glu Ala Gly Phe	
1330 1335 1340	
aca ccc gag ttc ttc aaa caa tct gac agt att cgg gat ctt ttt aat	12931

FIGURE 19

10 of 19

FIGURE 19

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tcgtcgtcgt cgcagcagca gccttctcca aaaagccgct caaaaaccgg caaaaaagcc 14007
tcaaaacttc caaatctcgt ctcgctcccc gtctaagcgt aaatctcagg ctccctccctt 14067
cgatccatat gtttcgtacg caccgcacgc gctcgtctct ccccgaggatt ccccgcgtaa 14127
gagaagatca cgtgggtgcg gtagtttagg tagtggtggt ggtgggtggtg gtggtagtag 14187
atctgttgga agacctgccc gccgatcagt gaagaaagaa gaatcagatg atgatgatga 14247
ggattattgc caagaagagg aagtgaagcg aaatccggca gaaaaggtec cgccgaaaag 14307
aaaacgagtt gtgtttgtgg aacctccaga ggtgaagccg ccggagccga aaaaacgagt 14367
tggtgttcct gtcctcatcat catcatcatc agctctaact actctccac aacaaggacc 14427
gctgatttcg ttgccaaaag ctgtgccagt tgtacctcg cccaacaac aagcaccacc 14487
acagctcatc aaaaagcacc agcagactct gtagcctgtg aagggtgctc agattagtgg 14547
tggtgggtgg ggtactccag gaccatccag gctatcgcca ggtccatcaa tcctccgaag 14607
aacggttggt ccaggcatag gcgctggtgg tgttggaagc ctaccgcttg tcagaatgcc 14667
tggtgcgccc ccatctcctg gctcgcaagc tcctgctcca ccgctgagaa gtggtgttgc 14727
tccaacagct cctgcagcag ctccacgcca gttcgtcgtt ccgctcgtcg gagttcgagt 14787
tatacgaag agaactccgg tcgccaccac catggtgcaa caacaacaaa gcccgagccc 14847
gttgatgttt ccagtcgggg ttgtgcaaa gcccgggcca tctggaccac caccacctgg 14907
acctccagat cgcccaggat ttggaatcta tgagaagccg agattctcac ttggatcacg 14967
aagaagccgt ggagattcgg gcccggaaga tccggcgcca ccacagccac caccaccac 15027
cacttctagg ccaccgccc aagcctaggc gctaggattt tccttttttt tttgttgatt 15087
tttgctcttt tttgctctc tcattgattt ataactcat tttgctttaa tatctccatt 15147
tttttgatg tgtggaattt ttttttttga aaatcgggaa aaaacgaaaa atttgaaatt 15207
tttggtgatt ttcagagaaa aatccgtttt taaatgaaaa aatcggaata attcagattt 15267
ttcgaaaaaa aaaaccgaga aaatttcaaa ttttcagttt tttttttcaa aaaatcgaaa 15327
aaaaaagtaa attttcagaa ttatcagcca agtttttgcg attttttgaa aaatttcaat 15387
ttttggcaat ttttgggaaa aaatcaattt ttaattcaga aaattggaaa aattaagatt 15447
tttcgaaaaa aaaaacgaag aaagtttcaa atttttagct tttttcaaaa aatcgaaaat 15507
cggaattttt ttaatttttc gaataaaaaa aatcgaaaga attccaaaac tttgcgtttt 15567
ttcttgaaat tatctgaaaa ccggaatttt ttttcaaaat tcgccatttt ttgcgaattt 15627
ttgtaatctt tttccgagaa aactcgattt tttaaatctt aataattcag atttttcgat 15687
tttcttttgt tccaaaaagt caaaaaccga acaattattt atttcaaaaa ctctaaaaat 15747
tttcaatttt ttggaaattt tcgggtataa aaaaaaccca tttttaaatc aaaaaatcgg 15807
aaatttttgt gatttttcga tttttttcac tccaaaaaaa tccacacag caaaaaataa 15867
actccgcgca ttttgagcg cacttttcaa ttttttaatt cttatcacga cgtcaaaatt 15927
cggttatttt tcacacacac acattttcct cccgagcggg tctttttttc atgagttctc 15987
ccatgttttg tttttatatt tgagacattt tttttgttg ataagtttca acttcttctt 16047
cttcttctga ctataaacgt ttttctccat gttttttgcc tgttttctgc cgattttttg 16107
acacccaaaa ttttttttca ttttcgctcg aaaatgcacg tcgttggtct tagctttggc 16167
aagtttttaa cactgatttt ctgggttttt ttttttttg cagaattttt cagagatagg 16227
gggctcattc cagcaggggt tcccactata tttcgcattt tttccaaaaa tttttgtatt 16287
ttcaaaaatt tccaaaaaga aaggggtttt ctttaccaaa tttttctcgc cacttttggc 16347
ttaatttttg ctttagagat tcgatcgaaa aaattgcgaa agtggcgaga aatctcactg 16407
gtttgatgtt tgacccctca ctatagaaaa tttgaaaaaa aaaaaaaaaa aaaaaataa 16467
gacgaaattt gttgaaatct tgcggagtt tgacgagtcg atggtggatt tttcttgaaa 16527
cgaatgaaac ggtgattttg gatcgagaa atatggcgaa aaatggtgag aaatgacgag 16587
gaggaggaag aagctgaaaa tctggaggaa caaaaattgt gtggaagtct cgggaagaaa 16647
ttagaattga aattttaaag tgttctgaga attttttgtg tgaaattttt ttaaatctgt 16707
agatcaaaaa tcaaaaaaaa aaatcagaac tattacgtgt ttatccacaa agatgagaaa 16767
aatcgccata tctggcgcgc aaatgaacc gcgggaagag acaaaactac tgtagttttt 16827
aaccaatttg ttagatttta cgagctattg cgtcatcgaa ttgaatttaa ttttcaggcg 16887
tttcacacgt ttttatattg aaatttatct atttattgaa tcaatcttaa aagaaaacac 16947
aaaaaatttt ttttaaaaaa tgcgggtcaa aattaaattc aattcgatga cgcaatagct 17007
cgtaaatcta cacaaattgg ttaaaaaacta cagtagtttt gtctcttccc gcgggttcac 17067
ttgcgcgcca gatattggtga tttttctcat ctctggataa acacgtaata acatttctcg 17127
gcacaataaa tttttgctga aacaagtgcg cgtctttgaa gagtactgca atttcaaaa 17187
cggttttttg gttggaaagc acagtacttt ttcaaagggtg cacaccttct cgaatttctc 17247
ttcgtgtcga gaccaagaat gccatttttc gattttttaa aaatcaaaaa aaaaattacc 17307

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52/92

FIGURE 19

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tttttaaagg tggagtaccg aaatttgaga ctttgttttt ttcggcccaa aatgggtccaa 17367
aactaccgaa tttcgtaatg agacgttctg aaaattttctc aaaaaacaac gttatggcgg 17427
tttaaagttc agcaaaaataa ggccccatttt cagctaaaaat caaaattttt tcccagcttc 17487
tcggtgtcac aacgcctgga acctaatattt tatttattca tcactttttg ataaatattg 17547
tggcttttta ttaggcgttt attttattga ttttaagctta tttatggctt ttgtggcggt 17607
acattttgta ccctaaaaac cataaatgta cttaaatcaa cgaataaacg cctaatacaa 17667
ggctacaata tttagtagaa agtgataaat aaataaaaat taggttccag acgttgcgac 17727
accgagaagt tggcgaaaac tttgatttta gctaaaaata agccattttc ccaaaacttt 17787
gagcgggtcat aacttttttt tgagaaagaa attttcagaa tgtctcatta cgaaattcgg 17847
tagctttggg ccattttggg ccgaaaaagc aaagtctcaa atttcagcac tccaacttta 17907
gcctttacct tggtgaaatt ttttaatctg tagtatactt ta'tttttggc cgactttttg 17967
aacacaaatt cgggtgttagt ttaaaaaaac aatcaaaact aacatattat ccagacgcga 18027
aatttttgtc ggtttttctc gcgccaaaaa gtacggtaac aggtttcggc acgatacatt 18087
tttgtaaaaa ggtgctgctc ctttgaagag tgtctaataa ttttcaactt tcgtttctgt 18147
tggaa'tttt tccaattttt catagatgtt ttcgatgaaa caaaaaatta acacaaaatc 18207
gtcgtgtcga gaccgaaaaa aattttgcgt ctgtgcaaca aacccggaat attaaagtag 18267
catattgatc caaattgccg atttgccgga aattttgatt ttcggcaata taccgatttg 18327
ccggaacatt tgattttctg gaatataccg atttgccgga atttttggtt ttcggaaatt 18387
tgccggaaat ttagaattcc ggcaatatgc cgatttgccg gaaattttga ttttcggcaa 18447
tatgccgatt tgccggaaat tttgattttc ggcaatatgc cgatttgccg gaacatttga 18507
tttcgggcaa tatgccgatt tgccggaaat tttgattttc ggcaatatgc cgatttgccg 18567
gaaattttga ttttcggcaa tataccgatt tgccggaaat tttgattttc ggcaatatgc 18627
cgatttgccg gaatttttgg ttttcggaaa tttgccgga atttagaatt ccggcaattt 18687
gccgatttgc cggaaatttt gatttccggc aatatgccga tttgccgga attttggtt 18747
tcggaaattt gccggaaatt tagaattccg gcaatatgcc gatttgccg aaattttgat 18807
ttccggcaat atgccgattt gtcagaagaa atcgtttgc acccacacgt gtattgattt 18867
gatttttct ag ata aaa ttc tac gac gag ctg gac gat atc atg cca atc 18917
Glu Ile Lys Phe Tyr Asp Glu Leu Asp Asp Ile Met Pro Ile
1515 1520

tgg ctt cca cca tca cca cca gat tgc gat gcg gat ttc gac ttg aga 18965
Trp Leu Pro Pro Ser Pro Pro Asp Ser Asp Ala Asp Phe Asp Leu Arg
1525 1530 1535 1540

atg gaa gat gat tgt ctc gat ctg atg tat gaa att gaa caa atg aac 19013
Met Glu Asp Asp Cys Leu Asp Leu Met Tyr Glu Ile Glu Gln Met Asn
1545 1550 1555

gag gct cgc cta cca caa gtt tgt cat gaa atg aga cgt ccg ttg gct 19061
Glu Ala Arg Leu Pro Gln Val Cys His Glu Met Arg Arg Pro Leu Ala
1560 1565 1570

gaa aaa cag cag aaa cag aac acg ttg aat gcg ttt aa tggtaatat 19109
Glu Lys Gln Gln Lys Gln Asn Thr Leu Asn Ala Phe Lys
1575 1580 1585

ttcaaaaaaa aatttttttg aaaaaattca attaaattcg attttgagca atttttatcg 19169
tgaagattgc ataattttga gattttgctc caagattttt gttaaattga aaaaaagaga 19229
tgtgcgcctt tatggagtac tgtagttttg aaaattgaaa ttacagtact ctgtttaaag 19289
gcgcacacat gtattacgta gcgaaaagaa aagtagta attagttaaa taagactact 19349
gtagcgcttg tgcgatttta cgggctctga attttatatg aatttttgaa aactagaaac 19409
atctcaaat gcataaaaatt accatttgaa cctcccgcga agtgattttg ttcgacgggg 19469
cgcgcttgca cgttttctat ttttaattta tttcaattttt tttgcttaat tctcaccgat 19529
ttttcatggt ttcagtttga ttttgatgga aatttgagaa caatatcaac ataaatgctt 19589
ttcaatcgaa aatgtgcatt tatattgaca ttttctccga atttccatca aaattaaact 19649
gaaaacacga aaaatcgggtg agaattaagc gaaaaaattg agttaaatga aaatagaaaa 19709
cgtgcaagcg cgctccatcg aacaaaatca attggcggga gggtcaaatt ggaattgtat 19769

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53/92

FIGURE 19

gcaatttttca aaaggtcgta taaaattttg aagaaagcaa attaaattta aaaaatcgag 19829
 ctcgtaaatc gacacaggcg ctaatttttca aaaaaataaa atgacaccca aaaaatcata 19889
 agaaaatcat aaataaatat tacgggaaca caaaactcag agaacccgta ttgcacaaca 19949
 tatttgacgc gcaaaatatg aaatatctcg tagcgaaaag aaaactaccg taattttaaaa 20009
 acattttaaat gactactgta gcgcttgtgt cgatttacga gatctcgatt ttctaaataa 20069
 atttttttaa aaatgatgtc agcgatatcc catttgactt tgtttcttcg tattattttc 20129
 tcatttttgc ttgattttat ttaattttat aattttattt aaaatcaagc aaaaacgaga 20189
 aaataatacg aagaaacgga gttaaatgga atatcgctga cataatttaa aaaaaaatt 20249
 taattagaaa atcgagatcc cgtaaatcga cacaagtagt catagtacag tagtcattta 20309
 actaattact gtacttttct ttcgctgcg agatatttca tatttttatt catattttta 20369
 tttattttca tatttttata tatatatata tatatatatt tcttggcggt ctaatgcagt 20429
 ttctctcaat taattcc a gac att cta tcg gca aaa gaa aag gaa tcg gtg 20480
 Asp Ile Leu Ser Ala Lys Glu Lys Glu Ser Val
 1590 1595

tac gat gcg gtc aac aag tgc ctt caa atg cca caa tcc gaa gcg atc 20528
 Tyr Asp Ala Val Asn Lys Cys Leu Gln Met Pro Gln Ser Glu Ala Ile
 1600 1605 1610

aca gca gaa tct gca gcg tct cca gca tac acg gaa cac tca tca ttc 20576
 Thr Ala Glu Ser Ala Ala Ser Pro Ala Tyr Thr Glu His Ser Ser Phe
 1615 1620 1625

tcg atg gat gat aca agc cag gat gcg aag att gag cca agt ttg act 20624
 Ser Met Asp Asp Thr Ser Gln Asp Ala Lys Ile Glu Pro Ser Leu Thr
 1630 1635 1640

gaa aat caa caa ccc acc acc acc gcc act act act act aca gta ccc 20672
 Glu Asn Gln Gln Pro Thr Thr Thr Ala Thr Thr Thr Thr Val Pro
 1645 1650 1655 1660

caa caa caa caa caa cag cag cag caa aaa tcg tcg aaa aag aag aga 20720
 Gln Gln Gln Gln Gln Gln Gln Gln Gln Lys Ser Ser Lys Lys Lys Arg
 1665 1670 1675

aat gat aat cga a cggtacggag gttactagcg aacaatttca agaaattttg 20773
 Asn Asp Asn Arg
 1680

aatttgtgaa aattcaattc cggcaatttt tcgatttgcc ggaactttta attttcgccg 20833
 aattgtcaat ttgccggaaa ttttgatttc cgccgaattg tcgatttgcc ggaacttttc 20893
 attttcggca aattttcgat ttgccggaac ttttaatttt tgacaaattg tcgatgtgcc 20953
 ggaaattttg attttcgaca atttgctgat ttgccggaaa tttcaatccc aacaattttc 21013
 cgatttgccg gaaatttcaa tccaacaat tttccgattt gccggaaatt tcaatcccaa 21073
 caattttccg atttgccgga aatttcaatc ccaacaattt tccgatttgc cggaattttc 21133
 aatcccagca attttccgat ttgccggaaa tttcaattcc ggcaattttt cgatttgccg 21193
 gaacttttca ttttcggcaa agtgtcgatt tgccggaaact tttcattttc gccgaattgt 21253
 cgatttgccc gaacttttaa tttttgacaa attgtcgttt tgctggaaat tttgattttc 21313
 gacaatttgc caatttgccg gaacttttaa tttttgacaa attgtcgatt tgccggaaat 21373
 tttgattttc gacaatttgc caatttgccg gaacttttca tttttgccaa attgtcgatt 21433
 tgccggaaat ttttaattccg gcaattttgc gatttgccgg aaatttcaat tccggcaatt 21493
 taaaaacact aaaaacacaa aattttcggt tttcccgttt ttcgatgttt cagcttttct 21553
 caaaaaaftg cgattccccg aaaaatcgaa acaattttcg ggggttaaac cgggaaattc 21613
 ctaaattcct atttaaaaga attgaaaaaa aactctcaaa attcc ag gct caa aat 21669
 Lys Ala Gln Asn

54/92

FIGURE 19

cga aca gct gaa aat ggt gtg aaa cga gcg aca act cca cca cca tca	21717
Arg Thr Ala Glu Asn Gly Val Lys Arg Ala Thr Thr Pro Pro Pro Ser	
1685 1690 1695 1700	
tgg cgt gaa gag cca gat tat gat gga gcc gaa tgg aat ata gtt gaa	21765
Trp Arg Glu Glu Pro Asp Tyr Asp Gly Ala Glu Trp Asn Ile Val Glu	
1705 1710 1715	
gat tat gca cta ctt caa gca gtt caa gtc gaa ttt gca aat gct cat	21813
Asp Tyr Ala Leu Leu Gln Ala Val Gln Val Glu Phe Ala Asn Ala His	
1720 1725 1730	
tta gtc gaa aaa tcg gcg aat gag gga atg gtg ttg aac tgg gaa ttc	21861
Leu Val Glu Lys Ser Ala Asn Glu Gly Met Val Leu Asn Trp Glu Phe	
1735 1740 1745	
gtg tcg aat gcc gtt aat aag cag aca aga ttt ttc cgc tcg gcc cgt	21909
Val Ser Asn Ala Val Asn Lys Gln Thr Arg Phe Phe Arg Ser Ala Arg	
1750 1755 1760	
caa tgc tca att cga tat caa atg ttt gtt cgg cca aaa gag ctc gga	21957
Gln Cys Ser Ile Arg Tyr Gln Met Phe Val Arg Pro Lys Glu Leu Gly	
1765 1770 1775 1780	
cag ttg gtg gct tct gat ccg att tcc aag aaa acg atg aaa gtc gac	22005
Gln Leu Val Ala Ser Asp Pro Ile Ser Lys Lys Thr Met Lys Val Asp	
1785 1790 1795	
cta tcg cat act gaa tta tct cat ttg aga aaa gga cga atg act acg	22053
Leu Ser His Thr Glu Leu Ser His Leu Arg Lys Gly Arg Met Thr Thr	
1800 1805 1810	
gag agc caa tat gct cat gat tat gga ata ttg act gat aag aaa cat	22101
Glu Ser Gln Tyr Ala His Asp Tyr Gly Ile Leu Thr Asp Lys Lys His	
1815 1820 1825	
gtg aat aga ttt aaa agt gtt cga gtg gcg gca aca cgg aga cct gtt	22149
Val Asn Arg Phe Lys Ser Val Arg Val Ala Ala Thr Arg Arg Pro Val	
1830 1835 1840	
cag ttt tgg aga ggc cct aaa ggt aga gga gga tgg ctt cat aat agt	22197
Gln Phe Trp Arg Gly Pro Lys Gly Arg Gly Gly Trp Leu His Asn Ser	
1845 1850 1855 1860	
cac tgc aac ttt ttc ctc acg agg gac gag aaa aag tgg ttt cta ggc	22245
His Cys Asn Phe Phe Leu Thr Arg Asp Glu Lys Lys Trp Phe Leu Gly	
1865 1870 1875	
cat ggc cga ggt gcc gac aag ttt ca gcggccattt atcttgcttt	22291
His Gly Arg Gly Ala Asp Lys Phe	
1880	
gttttcgcgc cgttttcttt cgtttttcac cgattttttt cgttttttct taataaaaact	22351
gataaataaa tatttttttg agatgctaaa aaaatttcca agtaaaaaaa tcatgtattc	22411
agtgggcatt cagcgggtgaa agtgggcatt gtaatatgat ggattacggg tatacaaaac	22471
ctaaactttt tctgaaacat gatacatgtg ctgcttaaat gctgagacta cctgattttc	22531
ataacgagac cgctgaaaaa gttttgaggt ttccaaaatt caactttttt qatqaaaaag	22591

FIGURE 19

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tcgagatttt cgcacaaaaa gttgaatttt gaaaacctca aaactttttc agcgggtctcg 22651
ttatgaaaat caggtaattt cagcatctaa gcatcatatg tatcatgttt cagaaaagtt 22711
taggttttgt attcccgtaa tccatctatt tacattgacc actttcaccg ctgcttgccc 22771
actgaataca taattttttc acttggaat tgttttagca tctggaaaaa gtattttatt 22831
atcagtttta ataagaaaaa acgggaaaaa gctgtgaaaa acaaaagaaa acaggcggaa 22891
aacaagcaa gataaatggc cgtgaaact tgtcggcccc tcggccatgg cctagaaacc 22951
acttttcttc gtccctcgtg aggaaaaagt tgcagtgata gtctaaaatt cggaggaatt 23011
ttttaaaatt ggaaaaaatt gtttaatttt tttttcttgg aaattggaaa atcacaattt 23071
ttcgattttt gtttgttaaa aaaaaaaaga aaattggcat aataaaacat ttcttttttt 23131
tttgaaaatt gggaacttct taatatcaga ttttttaagt aaqatttttt tgattttccg 23191
gaaattcgga aaacctgaaa attttcaaca tttcaaaata aaaatttccg tttttttttt 23251
ctgaaaatct ccaacaaaaa aaggtaaat cgtcagaatt attgttgga gtggcggttt 23311
ttcacgatta gagttcagta tttttcttc tgaatttcaa atttgaaaa aaatcgaata 23371
aactgtagaa aaatgataga aaattaacaa aaattctgat taaaggtaaa gggaaaatag 23431
accgtaatga ccgaatataa ctgttgaaaa tatcaacaaa aaaaattctg aattttttgt 23491
gactttttca atttttcaag aataaaaaaa acgaccgaat aaaaattttg aattcccgcg 23551
caaagtagtg actggttctg gccaatttac agtcttttta taaaagaaaa aatctagaaa 23611
aaccggcgaa tttagccaga aaacgcaaaa aattaaaaat gacgtcactc atttgcgcg 23671
ggaatacaaa ttttaattag ccgtttcttt gatttttgaa aaattgaaaa aaccattaaa 23731
aaatttagaa attttttga attttttaca gttttttatt cggtcattat ggggttattc 23791
aagtagtgtc ggaataattaa aaagtgtaga aaattacgt cacaactctg tattcaagta 23851
tataaaaaa tgtattttaa tacattttgc tacattactt gaataacccc attaggggtt 23911
attttcttta gagcaaaaaa aaacatgttt ggctctactc cacctttaaa tgaaaaaatc 23971
gacaatttgt gattttgcaa tttccagaaa aaaaagaaaa aagttgcttt ttggaaaaaa 24031
ccaaaaaag ccatttgaaa aattttattt tccaaaaaaa attattttgc agctctagaa 24091
tctcgaaatc tgcaatctct aaacggcgga atgccaccac gacacgagtc gagactcgcc 24151
gaattcgacg taaaaaccaa tattcgccgt gacgccgagg acattgtcac aatgtccgac 24211
gagtcgattg tcgcctatga agcagcaag aagaagctac tggccagtcg tcaaacaaaa 24271
ccctcaccac gtcaagatgt ccgattccat acgctggttc ttcggccgta taccgtacct 24331
gtgacaactg agtactcgge tgcaccttct cgtcgtgaaa tgcgcacgc tgttccaccg 24391
cttcagcctt cggctttatc tacgatttcc tcaattgctg ctgctgccac gtctgggcca 24451
cttaccatcaa ttcagcattt gcagtcgtcg tctacgggct tgggatctca gcaaaatttg 24511
caaaattcgc ataattctga gcaaagaaat aatgtgcaaa atatgcatca aaatcaatat 24571
aattcaagtc aaaatccgcc aataacctat cgacaaatcg gagcagcatc atcacacca 24631
catgatcaag gatctcaggg gcctggggga aaaccacaag cctatcacct ggtgcaacag 24691
ggatcacagc aacagcagca gcagcagcag caggcgacgt tacagcgaag aaatgcggcg 24751
gcggcgcgag ggtcgaatgt gcagtttatt cagcagcagc agcagcagca gcaatcgggt 24811
aaaaattgta tggatttata ggaaattata tgaatttgcg cggggatagc cccggcgaaa 24871
aacgggaaaa agcgacaatt taaaaaaaaa tcgtgtgaaa atctcaattt tttacaattt 24931
tgaaagtaat tttttattga aaaaagtgga atttaggcat tcatccagag cagggtggtg 24991
accataaaaa atttttggac caaaaaccaa aaacaaaaaa attgaaattt ccgaaaaatc 25051
aacttaagca tcaaaaattt tttgtttttt tttttgtttt ttggtttttt ttggtatttt 25111
gacgaaaaaa cgattttttg gttttttggt ttttcgagac caaaaaaacc aaaaaatcca 25171
aaaaaatgtt tgccgtgtct agtctcgacc tagacacggc aaacattttt tttttttgga 25231
ttttttggtt tttttggtcc cgaaaaacca aaaaaaccaa aaaaatcgatt tttcgtcaaa 25291
atacaaaaaa aaaacaaaga attcccagcc cctttcgcca aaattgccgg atattttcaa 25351
acctcaaaaa aaatttataa aggtggacta catcctgtgg ggaaattgct ttaaaacatg 25411
cctatgggct cacaatgacc gaatatcatg attaaaaaat tcaacaaaaa aattactaga 25471
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tttccgccaa ttttgattgt tcgatggagc gcgcttgctt tatttttttt tattcattga 25591
ttttttttt attagcatta tttcactgat tttcttcatt ttttggtgtg ttttggtggg 25651
aattgaaatg aaaaaaaaga agataaatgc agaaagtctg ttaaaagggtc attgaaatg 25711
cttaaaacgg caacaagctt gaaatttgta tattttacac agttttacgc attttcaatg 25771
actttttaac aaactttccg catttatctt gtttttttca gttcaatttc cattaaaaaa 25831
cacacaaaaa ahaatgaaga aaatcagtga aataagggtta ataaataaaa taaatgaata 25891
aaaaatgatc aagcgcgctc caacgaacga attcaattgg cggaatttca aatatggaat 25951
taggtgaaaa ctgagatttt tttttcaatt ttcaaaaaat catataaaat ctagaacct 26011

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56/92
FIGURE 19

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tttttgaatt ttttaatcat gatattcggg cattgtgacc ccataggcgt gttttaaagc 26071
aatttcccca caggggtgtag tccacctttg acgagggttg aaaaatgtccg gcaatttttg 26131
cgaaattgcc ggaaacttga gatttttcag tgaaaaattc caaatttcat gtggaaaact 26191
gtttttttgt tttttgaaa atgcaacaaa aaaaactatt tggcgcgaaa acgcggatag 26251
ttttgccaat tttcaaggat tttccgctat ttttaatgtt tttatgccga attttacttt 26311
aaaaaatcat aattattcgg aaaatgctcg aagagcattt ccaattgtct gtggagcgcg 26371
tttgactaat cagataatat tccaggcggg caaggacaaa gcttcgttgt catgggctcg 26431
cagagctcat caaatgatgg acaagggtgga gcacgcagcg tcggaggagg aggaggagga 26491
tcacaacagc ctcaccagca gcagcagcag cagccacaac aaagaatata gtacattcca 26551
caagttaccg gtacgcgaaa taacgggtgga ggtggtgga gaggaggcta cggtagtaca 26611
ctggtcatgc caagaggagg acgtgttgct aggggttgga gaaatacaaaa atcgcgaaaa 26671
aacggcattt ccggcttccc gaccaatcag cgatttgctc cgccacttt cggaaccaatc 26731
cgctgaccga ggcatttgat tgggttgaaa ttgggcggag cagcgaattg ctgatgcgaa 26791
atacgggaag ttctcatttt gatggaaatt ctgcaaaatt ctttaaaaaa aacaaaatct 26851
tctcaaatcc ggaaaaaatc acaaaggaaa tcgaagaaaa tcgcgatttt tgattccccg 26911
accaatcagc gatttgctcc gccacttttt gaaccaatca gcgttcgagg catttgattg 26971
gttcaaaaact gggcggagca gcgagttgct gattggattt ttcagttttt aaatttttaa 27031
agcttttttt aacggaaaaa ttcgagaaaa ccatagattt tgatgagaaa tgatgaaaat 27091
tttcatgaaa aaatggaaaa atgattggaa attaatcaaa aaatcttgaa aaaaaatttt 27151
ttttcagaga aaatgcttca tttttggctc tgaaacgcct cttttttatt tgtgcctccc 27211
cgaccaatca gcaatttgct ccgccacttt ttgaaccaat cagcgaccga gcgatccgat 27271
tggtttgaaa ttgggcggag ctaaaatgat ttttaaaaaa ttcccgattt gtttaattca 27331
gaaattttaga aaaaagaaat atagaaaaaa aatagaaaaa aattaaaaaa aaaaaaaca 27391
aaaaatcgga aacgtcggaa aatattacga aaaaaatttt ttttaattgat tttttttcga 27451
aaaaaactaa aattttaacc aaaaattcaa agaaaaaatt tgtttttgat tttttttcgc 27511
aaaaaaaaaa aaattttaac caaaaattca aaaaaaaaat gtttttcttg atttttttcc 27571
aaaaaaacta aaattttgac caaaaattca gcaaaaaaaa aattttttta ttgatttttt 27631
tttcgaaaaa aaataaaatt ttaacaaaaa attcaaaaaa aaaatttttt attgactttt 27691
ttcgaaaaaa actcaaattt taaccaaaaa ttcaaaaaaa aaaatttttt ttttgatttt 27751
ttccgaaaaa aactaaaatt ttaacaaaaa attcaaaaaa aaaatgtttt tcttgatttt 27811
tttccaaaaa aactaaaatt ttgacaaaaa attcagcaaa aaaaaaattt tttaattgat 27871
ttttttttcg aaaaaaata aaattttaac caaaaattca aaaaaaaaat tttttattga 27931
cttttttcga aaaaaactca aaattttaac aaaaattcaa aaaaaaaaat tttttttttg 27991
attttttcgg aaaaaaacta aaattttaac caaaaattca aaaaaaaaat tttttttgat 28051
ttttttccaa aaaaaactaa attttgacca aaaattcagc aaaaaaaaat ttttttaatt 28111
gatttttttt cgaaaaaac taaaaatttg accaaaaatt caacaaaaaa aaaatttttt 28171
attgattttt ttcgaaaaaa actaaaattt tgacaaaaaa ttcaacaaaa aaaaattttt 28231
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atatccaatg tcgtcaaatt ttgtgccagt acgtgttcta ccagccacgc aacaaggaca 28351
acaacgaatg atgacaggac aacgtcgtcc ggctccagcg cccggtactg tcgccgcaat 28411
ggtgttgccg aatcgaggag ctggtggaat tccgcaaatg cgcagtttgc agtgagtttt 28471
gcacggaaat tggacgattt tcagcgaaat tttcgggaaa aatggctatt ttgtgtttga 28531
aattgcgaaa tttcacgatt tcgtcttaaa tacgggtgcca acctaccca tgacggtttg 28591
atctacaaaa aacgcgggaa tttttcacac aaaaatatgt gagacgtctg cacgttctta 28651
accaatcggg tgaaaaactc gccgcatttt tgtagatcta cggtagatca ctgcagattt 28711
taagagagaa aaataaataa ataatccac aagggtttta aaattttttt ttcaatcgta 28771
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gcttcaaaat tacggtaccg ggtctcgaca cgacattttt attgtgtaaa atacacaatt 28891
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gaaaaaaaaa agtttcgaaa ctgcagtact ctttaaaggc gcacacatgt atgtatttat 29011
aaaaaatgtc gtgtcaagac cgtacttttg gctcacaatt tgcaaaaatat tgcggaattt 29071
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aaaaaatatt ttttaagggt gactacgctc agtggggaaa ttgcttttaa acacgcctat 29191
gaggcccaa tgactgaata tcatgattaa aacaatacaa aaaaattttc tagattttat 29251
atgatttttt gaaatttga aaaatcacag ttttcaccta attctttttg aatttccgcc 29311
aattggatta gttcgggtgga gcgcgcttac attattttta attatttatt ttattttatt 29371
tcgttatttg actgattttt ttcatttttt gtgtgttttc ctcggaaaaa ggaagaaata 29431

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57/92
FIGURE 19

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aacaagacaa atgcaaaatg tttgttaaaa agtaattgaa aatgcgtaaa actttgatat 29491
tctgagttcc gacgacaaca agcctgaaat tagtatattt cacagttttt ctcattttca 29551
attacttttt aacaaacatt ttgcatttgt cttgtgtatt tcttccattt tccgaggaaa 29611
aaacatagaa aatgaagaaa atcgggtcaaa taacgagaat aaataaaaatt aattttaaaa 29671
aagatgcaag tgcgctccac cgaacaaatc caattggcgg aaattcaaat atggaattag 29731
gggaaaaactg tgatttttcc cattttcaaa aaatcatata aaatttgaa aatttttttg 29791
aattttttta atcatgatat tgggtcattg gcgccccata ggcgtgtttt aaagcaattt 29851
ccccactgag cgtagtccac atttaatttt ccaaaacagc acatgctaata cctccaagtt 29911
attccagacg aggcagttac accggcgggt gtggtcagca acgaatcaac gtgatgggtc 29971
aaccacaaca aatgcgcagc aacaatggcg gtggagtcgg tggcgaaggga ggcctccagg 30031
gtgggtccagg aggtccgcaa ggaattcgtc ggccactcgt cggacggcca ctacaacgag 30091
gagtcgataa tcaggcggcg acggttgctc aggtcgttgt tgctccgceg caaggaatgc 30151
agcaggcatc acaaggacca cccgtacttc atatgcagag agcggtttcc atgcaaattgc 30211
cgacgagtca tcatcatcaa ggccaacagc aggtcctctc gcagagctca cagcaggctt 30271
cgcaacaggc tcccacatcg gattctggga cgagtgtctc gccacgacaa gcaccaccac 30331
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taatttctct cctatttttt tcttcgttgt aagattattt gtcccccaac caagggtgtc 30451
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tatattttta taaaaatcta aaaagttcgg cttttgactt ttgaaataat cgaaatggtt 32611
tgtttttaaa tttgaaaaaa tataaaaaat tcgatttttt caagataaaa agcgaatttt 32671
tttgaatttt tttcaaatcg taaaaaatgt ctgtagtttt tttaaagact ctcataaaaa 32731
tctgaaatgt tcgatttttt atttttaaaa taatttttaa aaaattttta tattttttat 32791
cgtgcgaatt ttttaccac tataatttgg aataattttc aqatctcaa aatatccac 32851

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FIGURE 19

aatcgcgcaa	atâtgccagg	aagcaatgaa	gattggataa	agaaggagggt	cgaggaccag	32911
gacaccaacg	ccaacagctc	gagctccagc	atagccgtct	cgcgtcagct	cgaagggaaat	32971
tctgctgttc	ctgacgccat	cgaccttctg	tcttctcaaa	tcaaaagaga	agttgaagag	33031
gaggatgatk	gcaacgatga	gactggaccc	cgttcggagc	ccgtggatgt	taagccgtct	33091
ccaaaacgcc	caacgaagag	gtcagccgag	acctggacga	cggtcggcg	ccaagcaaga	33151
aacggcttac	ggcgggagac	ggttcaactc	atcgattcgc	gtatgtgaat	gttggagtcc	33211
gccatccata	cgatccacgc	catcttgtca	tggaaaacttc	attgaatgaa	attaggtaag	33271
gaattattga	aaataattat	tâtatatcca	ttttaattca	attttttttt	tcagaatcga	33331
agatttcgaa	ataatccagt	atcttccagt	gcccttcagg	acttcgattc	ccatgaagct	33391
agtgatcttc	gcagtgaagaa	gtgaagaatc	tgccgagaag	atccgctcgt	taatcgatcc	33451
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gctgacggtg	gaggatttcg	tcaaggcaca	cataatggcc	agcaggtaag	ctttcgaaca	33571
tacttaattt	tttaaaaact	aaaattcagc	gcaaccgatg	acgtgccata	tgaggcagcc	33631
atggcggatc	gagaatcgct	caaacaagct	gtaaatgatg	ccagctctct	gaaaggcttg	33691
aaggaggtaa	taatttagaa	atgacagaaa	atgaaccgtg	atgacgaaat	acatctgtaa	33751
aaaaattata	aaaaattcta	agctccgttt	ttaatttttt	ttttcagtta	tattctgtca	33811
tagcggccta	tttctctgga	aaaaaaaaatc	caaaatagcc	tcaaattcgg	aattatgctt	33871
cgattttttt	tctgcggtag	tctgaattt	aagacgattt	tgaatttttg	tagctgcctt	33931
tcgccacaat	tacgttaaac	atttcagagc	atgtcgaaag	ctggatggag	gacgtgagt	33991
aagatgcgga	aagatctcaa	tggagcctga	tgatccccct	cccagcacac	aagacagctt	34051
taattttgtg	tctgtatagt	tttatattaa	gttttgatga	taatgaattt	ttttacggtt	34111
ttatccatca	cttggctcga	ttgaagctcc	tattgtgcag	cacacacggc	gtgtaaaatta	34171
gtgcatctaa	cctaggaaat	gcgatttcta	ggccatggcc	gaggatccga	ctagatcttt	34231
tttgatggtg	tttgtagaga	gttaaatttc	attttggagg	gaaattgaag	gaaattgaaa	34291
gagaaattaa	tttaataata	ttaatttgat	ttaaattgacc	agaacaaaac	aaataaaactg	34351
aatgacaagc	caatcgatat	tcgtccagac	tgggatgatg	ttatatgaac	tctttcacct	34411
gaaacattta	agttttttta	ataaaaagagc	aagcgcgctc	aaacgcgaaa	acgctcgatc	34471
cacttaatat	ggattttgtg	ccgattcatt	tatttcaagc	tatgctcggt	tttttctgtt	34531
atgtttcatt	aaaaagaccg	aaaacataac	aaaaagtgcc	tgaaaacgaa	aaaaaacccg	34591
cgacattaat	tgaaaaattc	aaaactacaa	tttcgccgcc	aaaacccaac	gagacccaaa	34651
gtttcagcgc	ggagcgttcc	cacttggccg	tggagcgcgc	ttgtatataa	aaggacttaa	34711
ttttttaaaa	tacttaccgc	agttacttcc	aatgtatgtc	aaattcactc	gattctccat	34771
tgcagggtta	ctaaaaatatg	ctccaaatag	ttggcaaggc	gttgacttga	ataaatcggg	34831
atgggttatct	tggatgattg	cagttcgatt	tccttttgta	attatgttct	aaaaagtcac	34891
tgtaatcatt	taaaagtgga	gtagcgccag	tggggatttt	gtctaaatgc	acttattatg	34951
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cctgtcaaaag	ttttggcaaa	ttggcaaaat	tttgaaaaat	gcgagctttt	gaggtaattt	35071
aaggaaatgt	cgcattgttc	gacccttaca	attatttaat	acagataatt	taaacaaaat	35131
taaaacataa	aaatgtagaa	attttttttg	ttttggctga	tttccaaaat	tatgagtggc	35191
aaaaactgag	taattgccac	tttttgacag	taaaataaaa	atgttcaaaa	ttttttgaaa	35251
cgttttatca	tgatatttgg	ccattatggg	agcaaatgag	tggtttatct	attttttcac	35311
tggcgtact	ccacctttaa	gcattgtctgc	ctcaccataa	tcccatttaa	tccaacggtt	35371
cttagatttg	gattcgaata	tatttgaatg	actggaaaat	atgttacggt	accattcaat	35431
gcaccaatat	aagtcatttg	atcgagaaaa	ttcaaactcg	tgagatttgt	gtttctgata	35491
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aaatcaggat	gaaggttttc	aaaattgaag	tattgccttt	tattgtatgt	actgtattgt	35791
atcatactgg	tttgctcaac	tgtatctata	actttctgaa	attttatgtc	attattttca	35851
gaaatcgcac	taggcaggca	agcctgcctt	accgtagaaa	ttggcagtc	cagtcgaatc	35911
atttccgcat	tatcttgtac	attcaatgct	acactagcta	tatccgagtt	atattcgata	35971
gtttgcagggt	tttgtaaaaa	cgacaaaactc	tgtagattag	tgttccgaat	tgcaatagat	36031
cctcgaatca	ttgtgacatt	caaaaatgaa	tcataatcga	aggttgcat	aatattcact	36091
aaatttagac	cagaatctag	agttttgcat	ttggagtact	ccttaacatt	tgatacatta	36151
actttttcac	catcacatcc	tgaattttga	ctatttttat	actgttaaaa	aattgtttct	36211
caccacaatc	ctttaagttc	cctctgacaa	tgagctcatt	atacatgtgt	aaaaaqccgc	36271

FIGURE 19

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catcacagga aaattccagt ttccgattat tctcgattct aatatcacac gcctcgatac 36331
cccgatcacg gtacaagtag agatcgtaga gcacactggg gtcgtttaat tgtgaattgt 36391
ttccgatgta aacaccgtct gaaatctgaa gtttaagaaa aaattaagta agttttaatc 36451
tacatggtga tccgtttttg ttgaaagtat caaaaaatta actggagtca gaatgtctca 36511
tttcgttttg atcttcaaaa aatgcgggag ttcagaccta gacatctcgt ctgatttcgc 36571
atggttaaga gcgttctgac gtcacaattt ttctgaaaaa atattcccgc attttttgta 36631
gatcaaatga aaatgagaca gcctgacacc acgtggagtt ccttatatac aaaaaagttg 36691
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actaaaatcc acttttttgt ttcagccgct ccgcaagcag cttcgtcgag gtcatggcag 36811
cggccgagtt tcccactccg ctgaaactcg gcacttaata tatgaacgac taagctagca 36871
gggccgccat tctaccttac cagcaaaaat gaattcggtc acttacacac atcacacacc 36931
acattaaagt ttcttttttc ttgtgcagct gtaaaaaccg aaaggcttgt cagactagta 36991
ttctcaatat taaatc                                     37007
```


FIGURE 20A

ssl-1 Predicted exons:

<u>Exon</u>	<u>Position in genomic sequence (inclusive)</u>
1	1001-1281
2	1923-2027
3	2084-2312
4	4420-5205
5	5855-6487
6	7685-8515
7	9700-10184
8	12211-13165
9	13643-13726
10	13796-13939
11	18879-19101
12	20449-20735
13	21661-22273

Figure 20B

ss1-1 cDNA

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atgccggcaa caccggtgcg tgcttcaagt actcgaataa gcagacgtac atcatcaaga 60
tcagtggctg atgacagacc atcaacttcg tctgcggtgg ctccacctcc ttcacccatt 120
gccatagaaa ctgatgaaga tgcggtagtt gaggaggaga aaaagaagaa aaagacatca 180
gatgatttgg aaattatcac tccaagaact ccagtcgacg ggcaattcc ctacatttgc 240
tcgattcttt tgactgaaaa tcgatcgatt cgcgataaat tggttctgag cagcgggtcca 300
gttcgtcaag aagatcacga agaacagatt gctcgagctc aacggataca gccagttgtc 360
gatcaaattc aacgagtcga gcaaatcata ctcaatggtt cagtggaga tattctgaaa 420
gatcctcgat tcgcagtaat ggcagatctc acaaaagaac caccaccaac acctgcacct 480
ctcctccaa tccagaagac aatgcaaccg attgaggtga aaattgagga ttcagagggc 540
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agagccgcca aaagagaagc gcatgtattg gctcgaatcg ccgagctccg taagaacggc 660
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aagcgaaaaa tcgccaaagt tatagctcac gccattgcga aacagcaccg cgacaagcag 840
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acggaagagt cggaggacga aggtgttatg agaagtcgtg ttctgccaaa accaattaat 2880
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caaacttcat gcattcgttc aaaaaccgtc gtaataacag ttccactgac catctccacc 3000
gatcgaagtg gttttcattt taatatggcc aatgttggaa gaggtgttgt tcgtttggat 3060
gattcagcac gtatgagccc accgctcaaa cgtcagaagc tcaccggaac tgcaacgaat 3120

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Figure 20B

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gccgacaagt ttcagc
5656

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63/92

FIGURE 21

ssl-1 protein

<400> 3

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Met Pro Ala Thr Pro Val Arg Ala Ser Ser Thr Arg Ile Ser Arg Arg
 1           5           10           15
Thr Ser Ser Arg Ser Val Ala Asp Asp Gln Pro Ser Thr Ser Ser Ala
      20           25           30
Val Ala Pro Pro Pro Ser Pro Ile Ala Ile Glu Thr Asp Glu Asp Ala
      35           40           45
Val Val Glu Glu Glu Lys Lys Lys Lys Thr Ser Asp Asp Leu Glu
      50           55           60
Ile Ile Thr Pro Arg Thr Pro Val Asp Arg Arg Ile Pro Tyr Ile Cys
65           70           75           80
Ser Ile Leu Leu Thr Glu Asn Arg Ser Ile Arg Asp Lys Leu Val Leu
      85           90           95
Ser Ser Gly Pro Val Arg Gln Glu Asp His Glu Glu Gln Ile Ala Arg
      100          105          110
Ala Gln Arg Ile Gln Pro Val Val Asp Gln Ile Gln Arg Val Glu Gln
      115          120          125
Ile Ile Leu Asn Gly Ser Val Glu Asp Ile Leu Lys Asp Pro Arg Phe
      130          135          140
Ala Val Met Ala Asp Leu Thr Lys Glu Pro Pro Thr Pro Ala Pro
      145          150          155          160
Pro Pro Pro Ile Gln Lys Thr Met Gln Pro Ile Glu Val Lys Ile Glu
      165          170          175
Asp Ser Glu Gly Ser Asn Thr Ala Gln Pro Ser Val Leu Pro Ser Cys
      180          185          190
Gly Gly Gly Glu Thr Asn Val Glu Arg Ala Ala Lys Arg Glu Ala His
      195          200          205
Val Leu Ala Arg Ile Ala Glu Leu Arg Lys Asn Gly Leu Trp Ser Asn
      210          215          220
Ser Arg Leu Pro Lys Cys Val Glu Pro Glu Arg Asn Lys Thr His Trp
      225          230          235          240
Asp Tyr Leu Leu Glu Val Lys Trp Met Ala Val Asp Phe Arg Thr
      245          250          255
Glu Thr Asn Thr Lys Arg Lys Ile Ala Lys Val Ile Ala His Ala Ile
      260          265          270
Ala Lys Gln His Arg Asp Lys Gln Ile Glu Ile Glu Arg Ala Ala Glu
      275          280          285
Arg Glu Ile Lys Glu Lys Arg Lys Met Cys Ala Gly Ile Ala Lys Met
      290          295          300
Val Arg Asp Phe Trp Ser Ser Thr Asp Lys Val Val Asp Ile Arg Ala
      305          310          315          320
Lys Glu Val Leu Glu Ser Arg Leu Arg Lys Ala Arg Asn Lys His Leu
      325          330          335
Met Phe Val Ile Gly Gln Val Asp Glu Met Ser Asn Ile Val Gln Glu
      340          345          350
Gly Leu Val Ser Ser Ser Lys Ser Pro Ser Ile Ala Ser Asp Arg Asp
      355          360          365
Asp Lys Asp Glu Glu Phe Lys Ala Pro Gly Ser Asp Ser Glu Ser Asp
      370          375          380
Asp Glu Gln Thr Ile Ala Asn Ala Glu Lys Ser Gln Lys Lys Glu Asp
      385          390          395          400
Val Arg Gln Glu Val Asp Ala Leu Gln Asn Glu Ala Thr Val Asp Met
      405          410          415

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64/92

FIGURE 21

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Asp Asp Phe Leu Tyr Thr Leu Pro Pro Glu Tyr Leu Lys Ala Tyr Gly
      420      425      430
Leu Thr Gln Glu Asp Leu Glu Glu Met Lys Arg Glu Lys Leu Glu Glu
      435      440      445
Gln Lys Ala Arg Lys Glu Ala Cys Gly Asp Asn Glu Glu Lys Met Glu
      450      455      460
Ile Asp Glu Ser Pro Ser Ser Asp Ala Gln Lys Pro Ser Thr Ser Ser
      465      470      475      480
Ser Asp Leu Thr Ala Glu Gln Leu Gln Asp Pro Thr Ala Glu Asp Gly
      485      490      495
Asn Gly Asp Gly His Gly Val Leu Glu Asn Val Asp Tyr Val Lys Leu
      500      505      510
Asn Ser Gln Asp Ser Asp Glu Arg Gln Gln Glu Leu Ala Asn Ile Ala
      515      520      525
Glu Glu Ala Leu Lys Phe Gln Pro Lys Gly Tyr Thr Leu Glu Thr Thr
      530      535      540
Gln Val Lys Thr Pro Val Pro Phe Leu Ile Arg Gly Gln Leu Arg Glu
      545      550      555      560
Tyr Gln Met Val Gly Leu Asp Trp Met Val Thr Leu Tyr Glu Lys Asn
      565      570      575
Leu Asn Gly Ile Leu Ala Asp Glu Met Gly Leu Gly Lys Thr Ile Gln
      580      585      590
Thr Ile Ser Leu Leu Ala His Met Ala Cys Ser Glu Ser Ile Trp Gly
      595      600      605
Pro His Leu Ile Val Val Pro Thr Ser Val Ile Leu Asn Trp Glu Met
      610      615      620
Glu Phe Lys Lys Trp Cys Pro Ala Leu Lys Ile Leu Thr Tyr Phe Gly
      625      630      635      640
Thr Ala Lys Glu Arg Ala Glu Lys Arg Lys Gly Trp Met Lys Pro Asn
      645      650      655
Cys Phe His Val Cys Ile Thr Ser Tyr Lys Thr Val Thr Gln Asp Ile
      660      665      670
Arg Ala Phe Lys Gln Arg Ala Trp Gln Tyr Leu Ile Leu Asp Glu Ala
      675      680      685
Gln Asn Ile Lys Asn Trp Lys Ser Gln Arg Trp Gln Ala Leu Leu Asn
      690      695      700
Val Arg Ala Arg Arg Arg Leu Leu Leu Thr Gly Thr Pro Leu Gln Asn
      705      710      715      720
Ser Leu Met Glu Leu Trp Ser Leu Met His Phe Leu Met Pro Thr Ile
      725      730      735
Phe Ser Ser His Asp Asp Phe Lys Asp Trp Phe Ser Asn Pro Leu Thr
      740      745      750
Gly Met Met Glu Gly Asn Met Glu Phe Asn Ala Pro Leu Ile Gly Arg
      755      760      765
Leu His Lys Val Leu Arg Pro Phe Ile Leu Arg Arg Leu Lys Lys Glu
      770      775      780
Val Glu Lys Gln Leu Pro Glu Lys Thr Glu His Ile Val Asn Cys Ser
      785      790      795      800
Leu Ser Lys Arg Gln Arg Tyr Leu Tyr Asp Asp Phe Met Ser Arg Arg
      805      810      815
Ser Thr Lys Glu Asn Leu Lys Ser Gly Asn Met Met Ser Val Leu Asn
      820      825      830
Ile Val Met Gln Leu Arg Lys Cys Cys Asn His Pro Asn Leu Phe Glu
      835      840      845
Pro Arg Pro Val Val Ala Pro Phe Val Val Glu Lys Leu Gln Leu Asp
      850      855      860
Val Pro Ala Arg Leu Phe Glu Ile Ser Gln Gln Asp Pro Ser Ser Ser

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FIGURE 21

865		870		875		880									
Ser	Ala	Ser	Gln	Ile	Pro	Glu	Ile	Phe	Asn	Leu	Ser	Lys	Ile	Gly	Tyr
		885		890		895									
Gln	Ser	Ser	Val	Arg	Ser	Ala	Lys	Pro	Leu	Ile	Glu	Glu	Leu	Glu	Ala
		900		905		910									
Met	Ser	Thr	Tyr	Pro	Glu	Pro	Arg	Ala	Pro	Glu	Val	Gly	Gly	Phe	Arg
		915		920		925									
Phe	Asn	Arg	Thr	Ala	Phe	Val	Ala	Lys	Asn	Pro	His	Thr	Glu	Glu	Ser
		930		935		940									
Glu	Asp	Glu	Gly	Val	Met	Arg	Ser	Arg	Val	Leu	Pro	Lys	Pro	Ile	Asn
		945		950		955									
Gly	Thr	Ala	Gln	Pro	Leu	Gln	Asn	Gly	Asn	Ser	Ile	Pro	Gln	Asn	Ala
		965		970		975									
Pro	Asn	Arg	Pro	Gln	Thr	Ser	Cys	Ile	Arg	Ser	Lys	Thr	Val	Val	Asn
		980		985		990									
Thr	Val	Pro	Leu	Thr	Ile	Ser	Thr	Asp	Arg	Ser	Gly	Phe	His	Phe	Asn
		995		1000		1005									
Met	Ala	Asn	Val	Gly	Arg	Gly	Val	Val	Arg	Leu	Asp	Asp	Ser	Ala	Arg
		1010		1015		1020									
Met	Ser	Pro	Pro	Leu	Lys	Arg	Gln	Lys	Leu	Thr	Gly	Thr	Ala	Thr	Asn
		1025		1030		1035									
Trp	Ser	Asp	Tyr	Val	Pro	Arg	His	Val	Val	Glu	Lys	Met	Glu	Glu	Ser
		1045		1050		1055									
Arg	Lys	Asn	Gln	Leu	Glu	Ile	Val	Arg	Arg	Arg	Phe	Glu	Met	Ile	Arg
		1060		1065		1070									
Ala	Pro	Ile	Pro	Leu	Glu	Met	Val	Ala	Leu	Val	Arg	Glu	Glu	Ile	
		1075		1080		1085									
Ile	Ala	Glu	Phe	Pro	Arg	Leu	Ala	Val	Glu	Glu	Asp	Glu	Val	Val	Gln
		1090		1095		1100									
Glu	Arg	Leu	Leu	Glu	Tyr	Cys	Glu	Leu	Leu	Val	Gln	Arg	Phe	Gly	Met
		1105		1110		1115									
Tyr	Val	Glu	Pro	Val	Leu	Thr	Asp	Ala	Trp	Gln	Cys	Arg	Pro	Ser	Ser
		1125		1130		1135									
Ser	Gly	Leu	Pro	Ser	Tyr	Ile	Arg	Asn	Asn	Leu	Ser	Asn	Ile	Glu	Leu
		1140		1145		1150									
Asn	Ser	Arg	Ser	Leu	Leu	Leu	Asn	Thr	Ser	Thr	Asn	Phe	Asp	Thr	Arg
		1155		1160		1165									
Met	Ser	Ile	Ser	Arg	Ala	Leu	Gln	Phe	Pro	Glu	Leu	Arg	Leu	Ile	Glu
		1170		1175		1180									
Tyr	Asp	Cys	Gly	Lys	Leu	Gln	Thr	Leu	Ala	Val	Leu	Leu	Arg	Gln	Leu
		1185		1190		1195									
Tyr	Leu	Tyr	Lys	His	Arg	Cys	Leu	Ile	Phe	Thr	Gln	Met	Ser	Lys	Met
		1205		1210		1215									
Leu	Asp	Val	Leu	Gln	Thr	Phe	Leu	Ser	His	His	Gly	Tyr	Gln	Tyr	Phe
		1220		1225		1230									
Arg	Leu	Asp	Gly	Thr	Thr	Gly	Val	Glu	Gln	Arg	Gln	Ala	Met	Met	Glu
		1235		1240		1245									
Arg	Phe	Asn	Ala	Asp	Pro	Lys	Val	Phe	Cys	Phe	Ile	Leu	Ser	Thr	Arg
		1250		1255		1260									
Ser	Gly	Gly	Val	Gly	Val	Asn	Leu	Thr	Gly	Ala	Asp	Thr	Val	Ile	Phe
		1265		1270		1275									
Tyr	Asp	Ser	Asp	Trp	Asn	Pro	Thr	Met	Asp	Ala	Gln	Ala	Gln	Asp	Arg
		1285		1290		1295									
Cys	His	Arg	Ile	Gly	Gln	Thr	Arg	Asn	Val	Ser	Ile	Tyr	Arg	Leu	Ile
		1300		1305		1310									
Ser	Glu	Arg	Thr	Ile	Glu	Glu	Asn	Ile	Leu	Arg	Lys	Ala	Thr	Gln	Lys
		1315		1320		1325									

66/92

FIGURE 21

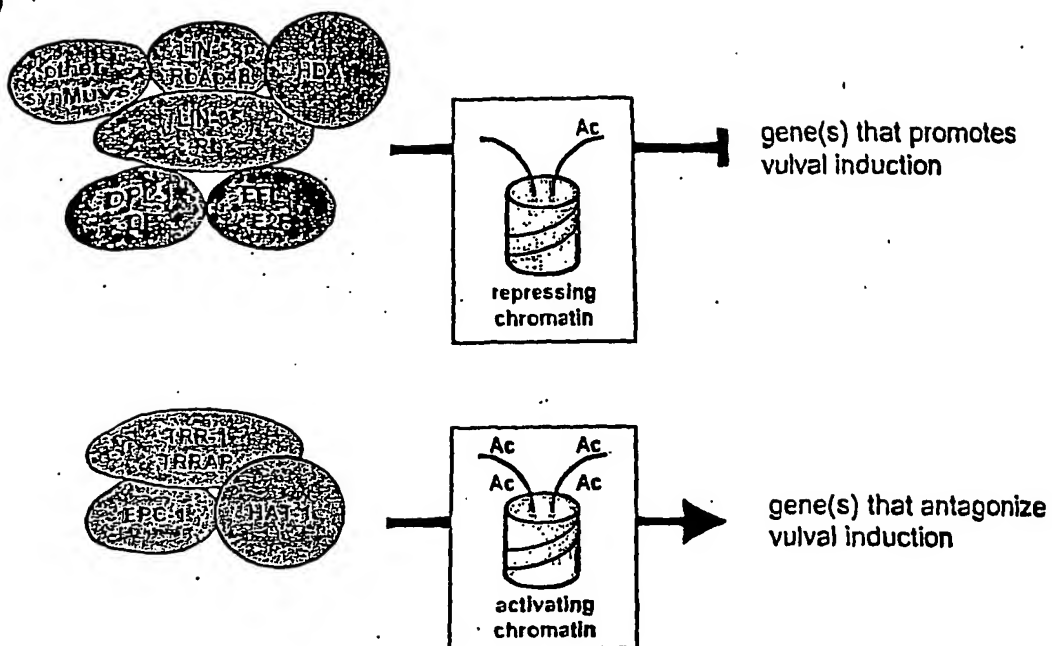
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 1365 1370 1375
 Glu Met Glu Val Ala Met Ala Lys Cys Glu Asp Glu Ala Asp Val Asn
 1380 1385 1390
 Ala Ala Lys Ile Ala Val Ala Glu Ala Asn Val Asp Asn Ala Glu Phe
 1395 1400 1405
 Asp Glu Lys Ser Leu Pro Pro Met Ser Asn Leu Gln Gly Asp Glu Glu
 1410 1415 1420
 Ala Asp Glu Lys Tyr Met Glu Leu Ile Gln Gln Leu Lys Pro Ile Glu
 1425 1430 1435 1440
 Arg Tyr Ala Ile Asn Phe Leu Glu Thr Gln Tyr Lys Pro Glu Phe Glu
 1445 1450 1455
 Glu Glu Cys Lys Glu Ala Glu Ala Leu Ile Asp Gln Lys Arg Glu Glu
 1460 1465 1470
 Trp Asp Lys Asn Leu Asn Asp Thr Ala Val Ile Asp Leu Asp Asp Ser
 1475 1480 1485
 Asp Ser Leu Leu Leu Asn Asp Pro Ser Thr Ser Ala Asp Phe Tyr Gln
 1490 1495 1500
 Ser Ser Ser Leu Leu Asp Glu Ile Lys Phe Tyr Asp Glu Leu Asp Asp
 1505 1510 1515 1520
 Ile Met Pro Ile Trp Leu Pro Pro Ser Pro Pro Asp Ser Asp Ala Asp
 1525 1530 1535
 Phe Asp Leu Arg Met Glu Asp Asp Cys Leu Asp Leu Met Tyr Glu Ile
 1540 1545 1550
 Glu Gln Met Asn Glu Ala Arg Leu Pro Gln Val Cys His Glu Met Arg
 1555 1560 1565
 Arg Pro Leu Ala Glu Lys Gln Lys Gln Asn Thr Leu Asn Ala Phe
 1570 1575 1580
 Asn Asp Ile Leu Ser Ala Lys Glu Lys Glu Ser Val Tyr Asp Ala Val
 1585 1590 1595 1600
 Asn Lys Cys Leu Gln Met Pro Gln Ser Glu Ala Ile Thr Ala Glu Ser
 1605 1610 1615
 Ala Ala Ser Pro Ala Tyr Thr Glu His Ser Ser Phe Ser Met Asp Asp
 1620 1625 1630
 Thr Ser Gln Asp Ala Lys Ile Glu Pro Ser Leu Thr Glu Asn Gln Gln
 1635 1640 1645
 Pro Thr Thr Thr Ala Thr Thr Thr Thr Val Pro Gln Gln Gln Gln
 1650 1655 1660
 Gln Gln Gln Gln Gln Lys Ser Ser Lys Lys Lys Arg Asn Asp Asn Arg
 1665 1670 1675 1680
 Thr Ala Gln Asn Arg Thr Ala Glu Asn Gly Val Lys Arg Ala Thr Thr
 1685 1690 1695
 Pro Pro Pro Ser Trp Arg Glu Glu Pro Asp Tyr Asp Gly Ala Glu Trp
 1700 1705 1710
 Asn Ile Val Glu Asp Tyr Ala Leu Leu Gln Ala Val Gln Val Glu Phe
 1715 1720 1725
 Ala Asn Ala His Leu Val Glu Lys Ser Ala Asn Glu Gly Met Val Leu
 1730 1735 1740
 Asn Trp Glu Phe Val Ser Asn Ala Val Asn Lys Gln Thr Arg Phe Phe
 1745 1750 1755 1760
 Arg Ser Ala Arg Gln Cys Ser Ile Arg Tyr Gln Met Phe Val Arg Pro
 1765 1770 1775
 Lys Glu Leu Gly Gln Leu Val Ala Ser Asp Pro Ile Ser Lys Lys Thr

FIGURE 21

				1780					1785					1790				
Met	Lys	Val	Asp	Leu	Ser	His	Thr	Glu	Leu	Ser	His	Leu	Arg	Lys	Gly			
				1795					1800					1805				
Arg	Met	Thr	Thr	Glu	Ser	Gln	Tyr	Ala	His	Asp	Tyr	Gly	Ile	Leu	Thr			
				1810					1815					1820				
Asp	Lys	Lys	His	Val	Asn	Arg	Phe	Lys	Ser	Val	Arg	Val	Ala	Ala	Thr			
				1825					1830					1835				1840
Arg	Arg	Pro	Val	Gln	Phe	Trp	Arg	Gly	Pro	Lys	Gly	Arg	Gly	Gly	Trp			
				1845					1850					1855				
Leu	His	Asn	Ser	His	Cys	Asn	Phe	Phe	Leu	Thr	Arg	Asp	Glu	Lys	Lys			
				1860					1865					1870				
Trp	Phe	Leu	Gly	His	Gly	Arg	Gly	Ala	Asp	Lys	Phe	Gln						
				1875					1880					1885				

FIGURE 22

A)



B)

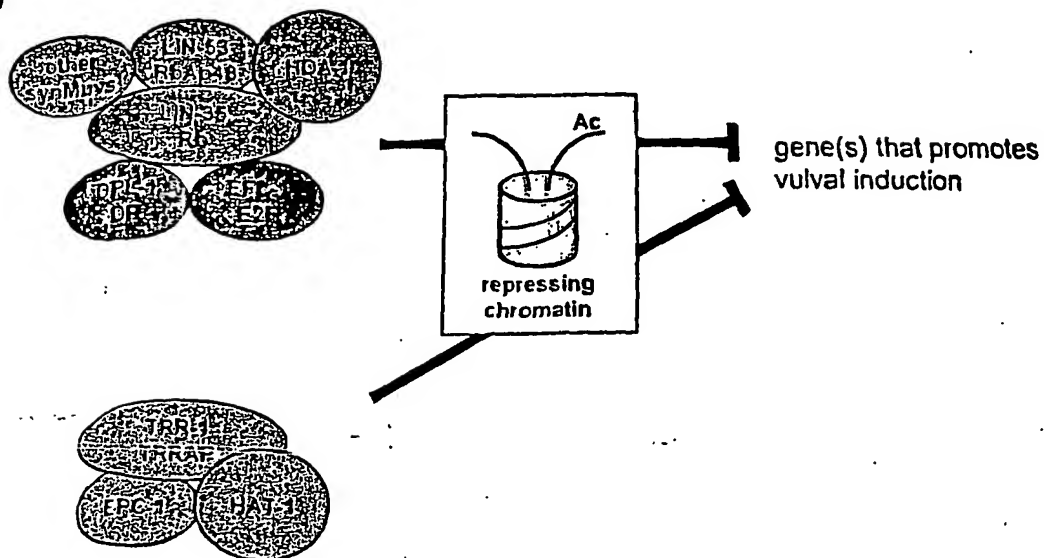


Figure 23

lin(n3628) genomic sequence (1 kb of upstream and downstream genomic sequence is included in this file).

<u>Exon number</u>	<u>Exon boundaries (inclusive)</u>
1	1001 – 1035
2	1920 – 2062
3	2114 – 2190
4	2241 – 2501
5	2551 – 2903
6	2955 – 3405
7	3497 – 3631
8	4227 – 4690
9	5293 – 6058
10	6696 – 7058
11	7609 – 8338
12	8771 – 8933
13	9511 – 10306
14	10774 – 10851

GTCAATGGAATTCTCGACGCGGATCTTGTTAGAGATGCCGTCGAGAGAGATT
TGATCAAATTGCGGTACGCTGAAACGGATGCACCAGTTTTACAGGTAAAATG
GAAATATACAACTCAAAAGTAAAATTTTATGAATTTTCAGATCAACAACTCA
CTATACACGGCATCCTGGGAGCAAGATCTCGGAACAAATATGGTTCTGCAGT
CAAAAGGAAAAGAGATGGAAGTGATTTCTGTGTACATCGACCATGATGACTGC
AGAAAAAGCCCTGTTGACCTCGTTAAGCACCGAAGGATCTACACTAGCCGCC
AATGCAGAGACTGCTCCGAAATCTGATCTCAGTCGAACTCAACCACGTCAAC
AATGATTTTCAAAATATAAATTAACATGAAGCTCTGAAATAAACTCATATAA
CTGCTAAAATAAACTGTTGCTTTTGAAACCAACATTTGTTAGACAACCTGCG
TCTCACAGTCATTTTTCAATATATTGGCGCCGCGCACACACAAAGAAGAAGA
ATTCGTCTCATGGCATGGCATGTGCAGTCAGCGGCCACCCTGTGTAACCACT
GCGTATCGCATCTTTCCACGTGTTTTTGCAATCTTGCTGTCACGTTTCAATTCCT
CGTACAACCATCTCTTCTACCCCGTTGCCTCCTCCACCATCTCATCTCAATTG
TGTCGTTGCCCTCCCTCTCCCAAGTCTTTCTGCGTCTCTTAGTGCTCTTCGAG
AAAAGAACGAGGAGAGCTGTGAGACGCTAGTAGGAAACGCATTCTCAATTC
GATATAGGCACATTGAGAGAGAGCGAGCGCGTTTCGACGTCTTCTAGCCTT
CACATCATCCAGACGACGTTACACGCACACACAGCCAACCCACCCTTCTG
ACAACGAATAGACGACGAAGAAGAGAAGAAGAAAAAGAAGAAGGTACCCA
TTTTTCATTCCCTTTTTGCCTCCACACTTCACTATTATCGATTTTGTGAGCGAG
CTCTAATGTTTCAACGCAAAGTGGTATTGCCTAAAAAGCGGTGAGAATTTGCT
TCAGACAGAAATTCGTTTTTTTAAACAAGAAAAATCCGGTTTCAATTGTCGTA
GAAGGTCAATTTTACTTTCAACGCTCTTCATTGACGGAAAACGTTTTTCTT
TCAAATTTTAAATTACAGAGGCATTTTACTCAAGGTTTGTTTTAAATTTAAATT
AAAAATAAATTTTAAATAGAAATATGGATAATATAAAATGTTTTCTTCAAA
AAATGCACTCAGGTTCAACAAAAATCGATAATTAAAAATACGGTCGCAAAG
GAGCGTCGTTAGCTGCTAATCAATGGTCTTAAAACGAATCTATCGATTTTGT
TGTA CTACACACGGACAAGTGCTCCACCGTTATTTTTTGAACGAGTGCGTTGC

FIGURE 23

AATTCCATCCCATTTTGACGTTTTCTTTTTTTTTTCATCAAATTTTTTAGCATT
TAAAGTAAAGTCAATGATAACCTGCAAATAATAATGTAAAATTCATTAATAAA
CCGAGAGAAAAAGTCTAAAGTCATAAATTTTTGATAAAAAAGTGATTTTCGA
AACTAAAAATCATTCAAATTAAGTTGAACCTGATTCTTCAATTTTTATTATA
TATTAAGGCTTGATCCACTCAAATAAAAGGAGTTTTTAATTGAGAAAAAAA
GCAAATGAAAAAATCGATAATTAATTTGGGCGCCAACCTAGATTTTAATATG
TTTTTGTTAGAAATTTGTATATTTTCATCACTCTCTGACTTTAAGCATTCTGTAT
TTTAAGGAAGTGTGAGCTTTCTAATATGTTTTTTTATTAAAAAAACATGTTTT
TAACAATCTCCCTGTCATCCCCATCACCTAATGCACTCAAATAATCAATAATC
ACAATACTTTTATTTTTTCTTGCGAAGCAGAAATGGTCCAAACGAGACGAAA
GACAGCTGCAGCTGTACAGGACGGTGGTGGCGTTAAGGAGAACAAAGCCAA
GCCACCTGCCCCTCAAACGCCTACAAAACGAGCAAAACGAGGTGCTCCCCCG
AAAATTAAGACTGGTGAGCGAATGACTATACGGAAGATTGAAAATTCACGTG
GAATACTTGCGAGATGCCAATACTTTGAATACGCCAAGCACTTCTTCCAACCTG
GTCGATGACAACTTCTCATTGAGTCTGAATCACAGGTAAATTGATTCTTTTC
TATTCAAAAATTAATCTAAACTATACATTCCAGGACTCGATTCTCACAAACGA
AGCCGACTCTTTTCTGGAAAAAGAAGTGGAAGAAATCGAAGATAGTTCAGAT
ATACTTCCCGATAAAATTAATTCTCCAGAAAAACCAAGTGTTTTGGTGAAGC
GGAGATCGAGTACGCGGTTAAAAGTGAAGACTGATGAAGATGAAAAAGATG
TTCCTGTGAACATAGAAGTAGCCGTTTTAGAAGAAAAATCAATTCAAATCGA
GCCAACATCTCCCGCTCACCCGGAAGATCCTCAGGTGAGCTTTTTTTAAAAAT
ATGTATTAATCAAATTCCTTCATTTCCAGCCTTCGACTTCTTCTCTTCCACTG
GTAGAACCAATTGAAGACATTGTGGAGCCAAATGAGCCAACAAGCTCTGCCG
ATCCTCCAGTATCAAATATTAAGGATGAGGATATTAAGAAGAAGAGCCACT
GATTA AAAAGCCAGCTTCCGATGAGTCAGAATCTATGGATATAGCTAACTCT
GAAAGTGGAAATGATTCCGATTCAAGTGAAGCTGATCCTAGGACGATACCAT
CTTTCTCTATACCTCTTCCCGACACACCACCTCCAAATTTTGCGAAAAGAGGA
GAAATACATGTAGATGTAGATCAGAAAAATTCCAAGCAATCAGGAGAATCAC
AATCGCCTTGGGAGCGGTAAGAATATTTATCCTAGCCAGGTGTTATAACAAA
ATTGAATAGTTTCAGAGCAAGAGAAAAAGTCTGCATCGAACCCATTGTCCTCT
CCAACAATGAGCCGACCCAGGATACACTTCCTTCATCCAGCATATCAAAGTTT
CACAAATGATTGAGTTTCACCTCTACCACCACCGCCACCAGAGCCGGCTCCA
GCTCGTGAAAAAGTGGAAAAATGGTGGTCCAACCTACTTTCAAATGACTTTCA
AAAAAGCTGCAAATATTCCTATCTTGAAGACATCGGCATTTGAACAACCATC
ATCACCTCCACCTTCCTCATCAGTTTCTTCATCAATTTCAATTATCTGAAGTGAA
TTCTTCTACATCGATAGCCTCCGAGTCTTCTCCAGCGAAAAGAAGCTCAAATT
TCGATTTAACTGCCTCAAATGAGCTTCCACCACCTCAGATGGTTGAACTTCCC
AAGCTCTCATTTTTCAATATGCCTCCAGCCGTTCCGCTCCGCAGAGGTTAGTTA
ACTTTTTCCCGGTTTCATGAAATTTAGCGGTATCTGTCCTCCTTTTGGTGTGT
GCCCTCACAACTAACCTCTTTTATCCAGGACGATTCTGCGATGACGTCGGAA
GAACCGATCCTTCTCCTCCGTTCTCCGAATTCCGCCACTCCTGATGATGATGC
ACTTTTCTCAGACCCCAACCAACCAAGATGACCGAATCAGAAATTCAA
GCACTGGTGAGCCAGATCACACATTTGATGTCGTGTGTGGAACCCAGGAAT
TTCAGACCGTTTTTCTTTACACCTCATCCCCTTTTGTGTTATGTTAACATTCT
TTTGTGTCTCAAACACTGCATGCTTTTGCACCTGGAAATTAATAATAATGCG
TTCTGGGATTTTGTGTGTTAAGGTGGAGTAGAGTTTGTGAGGCTAGAAAGTAT
GCCTTTTTCGTTTCTCCACTGCAAAATTTGTTTTGAAAAAACAAAAAATTA
CTAAAATTTGAAATTTACCAACTTGCCGTTGTCACAGCTGCTGAAATACAGT

71/92

FIGURE 23

TTTTATTGCATTTTACCCTTTATTGCATATTATTATTAGACACCTTTTAGGTC
AATAGGCAACCGAAAATATCCGAATTTGACTTAAAATGTACCTAAATTAAGG
AACTAAGTTGAGATATACGACTAAAAATGCAATAAATTGTGAGAATTATTGT
TATGAAATTCAGCCGTTTTAGGCTAGTTTTAGCCAAAAACCGACAACTCTAT
TCCAATTAATTTTCCACTCCTGCACCTCGATTAGTGATTTTTTTGAAGAAAAAA
AATTATCTTCTTATTTTCAGAAAGTAGCGACGGAAAAAGTGAATCAAGTAATT
GCTCGACGTGAAGATTCTGAAAAAGATGTACGTCACAGAGAAGATCGAGATG
ATTATGATAGACGACGTGACGACCGTGACAGAAGATCCAGAAAGACTGATTC
GGAACGAAATGATCAAAGAGGACGACAACGTGAAGATGATGAACGAAGAGC
TCGAGAACGAGAAAGAGAAGTTACGAAACGACATGATCGGGAAAGGGAAGA
GATGCGATTACAGAAACAAAAAGATGAGGAAAGAAGAAAGAAAGATGAAG
AGGAAAGGATACAAAAAGAGAATGATGAGAAAAAACAAAAAGAGGATGAA
GCCAAAATGGAGGAGGAGAAAAAGAAGATTAAAGAGGAGGAAATGAAGAT
TCCTGAATTTGAGTTGATTAGCGAATCAAATATTTGACGAGGAATGCGAAT
AAAAAGAAGACTGAATCCTTAACGTAAGTTATTATTTATAAATTTGACTTAAA
AATTGATAACTTTCAAATTAAGTGATTCAATAGACTCAAAGAATGAAAAA
CTAGAGTGCGCCTTTAAAGAGTACTGTAATTTCAAACCTTTTGTTGCTGCTCAT
TTTTCATCGATTTTTCTTAGTTTTTCGTTAAAAATAATTCAACCATTGGATTAA
AAAAAATTAAAAACACATAAATTTTATTTTGAAAAGTAATGAGAAAAACTAT
AGAAATTCGCCGAAAATTCTACAGCAACAAAAGCTCAAATTTACAGTACTTT
TTAAAGGAGCACATCTTTCTGAATTTAACAAAAATTCGGAGATTTTTCTTTTT
TTCGTGTTTTTCTGGCGAAAAAACGATTTTTTCGCTTTTACCGGAAACGGTATC
CGGAGGAAAAAAAACGAAAAAAGCGAAAAATTTTAAGAAGTTTCAAGAT
TAGTTACAACTCTTTTCAAAGCAGATTCTACAGTTTTTTTGGGGTTTTGCCA
AAAAATTTATGAAATATAATGTTTTTTAGACTAGAAAAATAAACTAATTTTAA
TTTTCAATCAAAGCTCATTATTATATTATATTATATAATTCAGTTGCGAAT
GCCATCGAACTGGTGGAACTGTTCCGGACAATACTTGTGTGAATCGTGCAAT
GCTCACCGAGTGCCCATCATCATGTCAGGTCAAATGCAAGAATCAACGATTT
GCAAAGAAAAAGTACGCGGCTGTTGAAGCATTCCACACTGGAACCGCCAAA
GGATGTGGACTTCGAGCAGTGAAAGACATAAAAAAAGGAAGATTCATCATTG
AATATATAGGAGAAGTTGTGGAAAGAGATGATTATGAGAAGAGAAAAACGA
AATATGCAGCTGATAAAAAGCACAAACATCATTATCTCTGTGATACTGGAGT
CTACACGATCGACGCAACAGTCTACGGAAATCCATCTCGATTTGTGAATCAT
AGTTGTGATCCTAATGCTATATGTGAGAAATGGTCTGTACCAAGAACTCCTGG
AGACGTTAATCGAGTTGGTTTTCTTCTCGAAACGATTCATTAAAGCCGGCGAA
GAAATCACATTTGATTATCAATTTGTCAACTACGGACGTGACGCTCAACAATG
TTTCTGTGGAAGTGCTTCATGTAGTGGATGGATTGGGCAGAAACCGGAAGAA
TTTTCATCTGATGAGGATGATGATATTGTGACTACAAGGCATATTAATATGGA
TGAAGAAGAAGAAGAAAAGTTGGAAGGTCTTGATCATCTTGGAATCATGAA
CGGAATGAAGTGATCAAGGATATGTTGGATGATTTGGTCATTTCGGAATAAGA
AGCATGCTAGGAAGGTTATACAATTGCGGTAAGCATTATTTGTAGAGAAA
ATTTAAAAATTAAAGATGGAGTACCGAAATCCGAGAAATATATTTAATTGAC
TCCAATTTTTCTCTGATTCGGAATTTTTAAATGAAAAAATTCAAAAAATTT
CCTTGATTTTATGTTTTAACTTGAAATTGCGAATTTCAATTTGTACAGATTTTTG
AAACGCCGAATTTTCGCGCCAGAGAAGCCATGTGTCGATTTTTGAGATTTGTG
TATATTTACAAGATTTTGAATCTTCATCGGATGCTGATTTGCGTTTTTTCATCAT
TATATTATCAAAAACTAACAATTTGTTCCGTTTTTACGGAAATTAACAATATA
GACTAGACATTTTCGTAAATATACACAAATCTCGTAAATCGACACATGGCGTC

FIGURE 23

TCTGGCGCGAAAAATTCGGCATTGAAAAATCTTATGCGGGCACTAATGAAAT
TCGTGATTTCAAGCTGAAATATAAAATCAGGGAATTTTCCTTGCATTTTTTCA
CTCAGAACTTCGGAATCAGTTGCAAATTTGGAGTCATTTGAAAATATTTCTCA
GATTTCTGGTACTCCACCTTTATTATAATTTTTTAAAATTTTTTAAATGATTTTTT
TTCCATGTTCAACAAAAAATAAAATTTTCAGTCTGCAATGACCGATTACTCTC
AACGTGTGGATGTCATTCAAGAAATCTTCTCCTCAGACACCTCCGTAAACCGTT
CAAAAATTCTATGCAAAAGAGGGAATGGCTACATTGATGGCTGAATGGTTGT
CTGAAGATGATTATTCGCTGGATAATCTGAAACTTGTTCAAGCTATTCTCAA
GCTCTTCACACTGAACTATTCGATTTCGTGCGCCAAAAATGATCGACTCTTACG
AGATTCTACATCAGATGGGTCAATGCGAAAAATGGATGAATATGTTGATATA
CAAGTGATAGCTGATTCACCTATTGCTTGTGTTGAAGATCCCGTACAGGAGTA
CAAGGATGTTTGCAAAGTTATAGAGGTATATACATATTAATTTTTTAAAAAAG
AATATTTTTTGCATGTCACAAAATATTTGGAAATTTTCCCGAAAAACCCATGA
AATCAAAAAACAAATTAAGTAAAAATTAATTCCTCCTACGAACATTTTTCG
ATTTTTTCGTTTTCCGATATTCCTTTTAAAAATCTGATTTAAAAAATAAACT
TAAATTTTAGGTCTTTTTGCTCCTTTTTAGAAGCAATTTATATGTTTTTTAAAA
CAAACTTAAAATTAGCATTTTTATGGGTAATTTTCTGAACACATTTTTTTTTTC
GAAAAAATGGCCAGAATTTCAACCACTTCTCCGTAAAATCGAAATTAATA
ATTTTTTCTCTATACATTTTTTCAAAAAAAGACTCCTCATTTATTGTATTAGATA
CAAATATATGTTTTCTCATCAAAATTTACGAAATTTGTTATAATTTGAATTT
TTTTTGTTTTTTTTTCGAAAAATTGAAAATTTTCTAATTTTGAAACGATATTAT
ACAATTTTCAGCGCCATCAATTTAACTAATTAATAATTTTCAGAAAGGTCTCGT
CGAAAACCTTCACAAGAGCCAAAGAGATGGCCTATCGGTTAAATCAATACTGG
TTCAATCGATCAGTGAGCTTCAAAATTTCAAAAAAAGATACGTGATCCTGTGC
CAAAAGATGTTCCAGTCAGACAAGAAGATGCTACAACATCATCACAACTCTCA
TGATAATAGTAGTAGAACTGTATCACCGAATCATCGACATCATTCATCTTCAT
ATTCAAATTCATGTTATCAAGAACGAGAACCATCTCATATACGATTCTTTAAT
AATGGAAATGATGTTTCATCAATATCGTTTTTGGAGGTTATCATGGAAATAACTA
CAATGATAACTATTTTCAGTAGAAGGCCCAATAAAGGATTCATATCGAGATCGC
CGTCGATTTAATGGACGTCGTTTCGAGAAGTCGATCAAGAAGTGTCTCACCAC
AGAACTATAAAAGAAGAAAACCTCGATGAACATGACAATAATCATCGTCAGC
GTTCTCCAATTCGTGATCGTCACACATCTCCCGGCGGCGAAAAGACTCCTAGC
TCGAATAATTCTGGAGAACGAACTATAAAAGACTGGATATTCGAGGAGCTC
GTATAAAACTATAAAAGAAGATTTGGAAGCTGCTGCTGCTGCTGCTGCTGC
TGCTGCTGTACCATCAGAAGTGCAAGCTTATCCTCATGAACATACAGCTGTAC
ATCAGAGTGTTTATCAGATGCCAGGTTATGAGTCTTATGGTTGGTTTAGTTTT
TTTAAAAATATCATTTACCAGGGTGCCATTTTTTAAAAATAAAAAATAACTCGGA
AAATATGTTTTTAAAAAATTTTCAGAATTTCTCTCATCAACATAAAACTTGATA
AAAATCGAATTTTTATTATTTTCTAAACATTTTTTTCGGTTTTTCCGAAAATCAA
AAAAAAGTTTAGAAAAATAGCAAAAAATCAGTTTATTAGAAATCAAATTTTG
TTCGTTTTTGATAAGAAAAAACATAAGAAAACATGTTATTTTCTTCTGAAAAAA
GAAAAAATCGAAAAATCTATGGCCTTTTGGCAAAATGTTTTGGACCAAAAA
ACAAAACAAATAGCATTAATAATTATTAGTTCTTTTGTTTTCTTCTAAAGTTAA
TTTTCTGAAAGTCTTGCTTGTCGTATATCAAATAAAAAACATTTTTTCAGGAGTA
TATGATCCTGTAAATGGTGTCTACATGTATCCTCATCCTGGCGCTGGTTACTA
TCCACCTGCCTATCCACAACAACCGATTATGTTAACAATGGACACTCTCCAC
CGAATGATCGTCTTGGTGAACCTTACGAGAAAGCCAGTATCGAGCAGCTAGC
GTGAGCATTTTTTAGTTTTAAACCTTTCGGATTTACCTAGAAAAATGTTACCTTT

FIGURE 23

GACGCAAAATTACGGTAGCAGGTCTCGTCGCGACCGAAATTTTTTCAGCGGAG
TACGGTAGCTTCCCATGAATTTTTTTGCTGAACCTTATCTTTCTGATAACAAATA
GTAATAAAACATGAAAACTGAATAAAAATTGATATCTTTACCTTATAGGC
TCTTTAAGGGCGCAGACACAAAACTGACCGGCTACCGTAATTTTTTCGTCAA
AAGTCACACATTTCTCAACTGGTGAAATCCGAAAAAATTGAAATTTTTACTAC
TCGTCCGACTGTTTAGAAAAAGATTAAAAAAGAAAAAAGAATGTCGGTT
TTTCGAATTTTCGATTTTCAAAGAAAAAATCAATATTTAAAAATCATTTCG
GTAATTTCCCTAAATTTGTAAATATAATTTCCAATAAATGTTTTTTGTTTTCC
GGAATTTTAATAAAAAATCAATTTTCGCGTAACAAAAATGCGAAAAAATGAC
TAGCCACTCGAATATAATAACACATGAAATAAAATTAAAAATTATTACAGTCA
ACGAGATGCAATTGTGAGACAAGAAGCTTGAGCTGATACGTATTCAAATCGAA
AGAAAACTGCTCAAAAAGAAGCGATCAAGGCCGCTTGCCGTCGTGCTAACG
AAGAAGAAGCTAAACGACAAGAGGCACTTGCAAAGACGAAATATGTTTGGG
CGATTGCAAAGTCAGAAGCTGGAGAGACGTATTACTACAACAAAATAACAA
AAGAGACGCAGTGGACAGCACCAACACCAGTTCAAGGTCTTCTCGAACCGGC
TTGTGGTGCATCTCCTGATACTACAGTTGTCAATTGCTGACGAGATTACTGAAG
AAGAGCAACAAGCTGAAGTTCTGGAGAAGCCGCGTGTGTTAAGGAAGAAG
TTATCGAGCCAGGTTCACAATCTGAACTCAAAAAGAATCTCCGGAGAAAGT
TCGAGTTGTTGTACCGAAAGTTGAAGTTGAAAGATCACCGTCGCCAAAATCT
TCTCGTGATCGTGAGAAGGATCGAGAGAAATCTCGTGAGAAAGATCGTGAAA
GAGATCGTGACAGAAGAGAAGGTTCAAAACATCGTGATAGTTATCATGGACA
TCGAAACGGCAGCAGTTCTGTCACTGAACGACGTATGCGAGAGTTCAAACAT
GAGCTGGAACGATCCACTCGATCTGCCGTTCTGTTCTCGTCTACAACATCAACG
TGACGCTTCTAGTGATAAGACTACTTGGCTTATTAAGTTAATATATCGAGAGA
TTTTCAAACGAGAAAGTGCGCAGAGTGGATTTGATTATCGATTCAAGTGAGAA
TACTGATAAGAAGGTAATATTATGGACCAAAAAATAAACAATTGAAAAAAA
AACCAAAAAAATCTGATGCTTGAATTTAAAAAACAATGAAAGAGTGCA
ATTTTTTAGGTTTTTTTGGTCTTTTTTTTTTGGA AAAACCAAAAAATAAATTTTTT
TCCAAAGTACCAAACTTCATTTTAAAAAATTTTATTTGACATAAAAATTGATA
ATTTAAACTAATTTGAACATTTTTCCGCAAAAATTATAGATTTTTCTGCCAA
TTTTAGATTTTAAACGTTTTTTTTTCGGACAATTAATGTTTCGAATCATCAATCA
GAATGAATATGATATCTGATGAAATTCAAAAATAATGCAATTTAAATAGAAA
ACGGTACAAAAGTTTTGAAAAATTTAGAAGAATTCTAAAAAATCCTGTCC
TTCAGGACAAAATTCAACCTTTTTCTCAAAACACAAAAATTACTTTATATTAT
TTTTCAGGTGAAAACTACGTCAAGTCATATATCGACCGAAAACCTCGAATCA
AACGATCTCTGGAAAGAATACTCTCGGCCATGAGCTTTATTTTTTAATTTAAA
TTTTATAAAAAAATGTTTATGCTTGTTTTTTTTCTCTATAGTTCCCTCCTATCCC
CCCCCTCCCCTATCGCCTAAAAATTGATCTCTGTCTGATTTACCGATTTCCGT
TTTATTTGATCCCATTTGAACGAGTATATCATCATGTTTCTGAACCTCAACGTTT
GCACATTTTATCCCCTAGTTTTATGTCCCCAGAATTGTTTTATACTATCCTGT
AATCCACCTCAAAATGACAGCCATGAAAAGCTGTTTTTCATGTTTTCTATTTT
CTTGTTGATCGTATTTGCGCGCGCTCTTTGTCGCGCAAAATTTTTTTTGTAATTA
AAAATGAATTACGGATGTTGAATTTTTAAATTTATTTTTTTAAAGAAAAATTG
TGGAAGTTTTTTCAGATTCTATACTGCTTATTTTTACGCTAAATTTTTTTTCGAA
GTCCCCTTTTTTCAAATCGAAGTGTAAGTTCGCTCCACGATCAATAGAGACTC
TCCGCCCTCGAACCATGGGTCTCGTTAGGTATTTGGCAGACTTACCGTAAATT
CAAATGTTTTATTACTTCGCGACTAATTTTTTTTATTCATGACTCAATTTTTTAT
CAATCCAACGAAAACTAATTA AAAACAACGGAAAAACATAACGAAAAATG

FIGURE 23

CTTGAAAATTGCAGACATTTCCGAAATTAATTAAATTCCTAACGAGACCCATG
GCTCGGGGGCGGAGTGTTTTTCGATTAGCCATGGAGCGCGTTGAGATATTCCT
AAATTTTTCTATTCAGATGTCGAATCAATCAAAACGGGTCACAGTGAGAATT
GAGCATTCTGAAGAACAACCTTTTTTCGAAAAGTAATTTTCAAATTTTGATCCAAA
GAAATTATTCGTCAATTTTCAGAGTTTTTAAAATTCCAACATCAAGAGCAAGA
AGATCGGAAGCTCAAATATGTTCTGCACAAAGCTCACGAGAATCTGAGAAAG
TGCCCATTCGAGATTCTGACAATTG

Figure 24 LIN(n3628) Protein

MFQRKVVLPKKRTEMVQTRRKTA AAVQDGGAVKENKAKPPAPQTPTKRAKRG
RPPKIKTDANTLNTPTSSNLVDDKLLIESESQDSILTNEADSFLEKEVEEIEDSSDI
LPDKINSPEKPSVLVKRRSSTRLKVKTDEDEKDVVNIEVAVLEEKSIQIEPTSPA
PEDPQPSTSSLPLVEPIEDIVEPNEPTSSADPPVSNIKDEDIKEEPLIKKPASDESES
MDIANSESGNDSDSSEADPRTIPSFSLPDTPPPNAFAKRGEIHVDVDQKNSKQSGE
SQSPWERAREKSASNPLSSPTMSRPRIHFLHPAYQSFTNDSVSPPLPPPPPEPAPARE
KVENGGPSTTFKMTFKKAANPILKTSAFEQPSSPPSSSVSSISLSEVNSSTSIASES
SPAKRSSNFDLTASNELPPPQMVELPKLSFFNMPPAVRSAEDDSAMTSEEPILLR
SPNSATPDDDALFLTTPPPPKMTESEIQALKVATEKVNQVIARREDSEKDVRHRE
DRDDYDRRRDDRDRRSRKTDSENRDQGRQREDDERRAREREREVTKRHDRER
EEMRLQKQKDEERRKKDEERIQKENDEKKQKEDEAKMEEKKKKIKEEEMKIPE
FELISESKYLTRNANKKKTESLTCECHRTGGNCSDNTCVNRAMLTECPSSCQVKC
KNQRF AKKKYAAVEAFHTGTAKGCGLRAVKDIKKGRFIEYIGEVVERDDYEKR
KTKYAADKKHKKHHYLCDTGVYTIDATVYGNPSRFVNHSCDPNAICEKWSVPRT
PGDVNRVGGFSKRFIKAGEEITFDYQFVNYGRDAQQCFCGSASCSGWIGQKPEEF
SSDEDDDIVTTRHINMDEEEEEKLEGLDHLGNHERNEVIKDMMLDDLVRNKKHA
RKVITIASAMTDYSQRVDVIQEIFSSDTSVTVQKFYAKEGMATLMAEWLSEDDY
SLDNLKLVQAILKALHTELFDSKANDRLLRDSTSRWVNAKMDEYVDIQVIADS
LIACVEDPVQEYKDVCKVIEKGLVENFTRAKEMAYRLNQYWFNRSVSFKIPKKI
RDPVPKDVPRQEDATTSSQSHDNSSRTVSPNHRHHSSSYNSCYQEREP SHIRFF
NNGNDVHQYRFGGYHGNNYNDNYFSRRPNKDSYRDRRRFNGRRSRSRSVSP
QNYKRRKLDEHDNNHRQRSPIRDRHTSPGGEKTPSSNNSGERNYKR LDIRGARIK
TIKEDLEAAAAAAAAAAVSEVQAYPHEHTAVHQSVYQMPGYESYGVYDPVNG
VYMYPHPGAGYYPAYPQQPIMLTMDTLPPNDRLGELYEKASIEQLAQ RDAIVR
QELELIRIQIERKTAQKEAIKAACRRANEEEEAKRQEALAKTKYVWAIKSEAGET
YYYNKITKETQWTAPTPVQGLLEPACGASPDTTVVIAD EITEEEQQA EVLEKPRV
VKEEVIEPGSQSETQKESPEKVRVVVPKVEVERSPSPKSSRDREKDREKSREKDR
ERDRDRREGSKHRDSYHGHRNGSSSVSERRMREFKHELERSTRSAVRSRLQHQR
DASSDKTTWLKLIYREIFKRESAQSGFDYRFSENTDKKVKNYVKSYIDRKLESN
DLWKEYSRP

Figure 25

lin(n4256) genomic sequence (1 kb of upstream and downstream genomic sequence is included in this file).

<u>Exon number</u>	<u>Exon boundaries (inclusive)</u>
1	1001 – 1096
2	1166– 1453
3	1501 – 2199
4	2298 – 2730
5	3234 – 3847
6	4148 – 5778
7	6111 – 6333

GCTTGCATCGAAACTCTTCTCATTATTTACGTGATGATCACATCTTTCGTTGGG
 CTGTACTCCCTTCCGGTTCTTCGTTCTCTTCGACCTGTTTCGAAAAGATACTCCA
 ATGCCAACGATAATTATTAATTCTTCAATAGTTCTTGTTGTTGCATCCGCTCTC
 CCAGTAGCTGTTAACACAGTTGGAATGACAACCTTTTGATCTTCTCGGCTCCCA
 CTCATCGCTCCAATGGCTTGGATCATTTTCGAGTCGTTGTTGCCTATAATACTCT
 ATTCGTCTGTGTTGTCTGTCTGCATTTCTCTCAATCAATTGACTGCTTCAATGAG
 AAGGCAAATCTGGAAGTGGTAAGCTGTGCAATTTAAAGTTTAAATTCTTATTA
 ATTTTTTTGCAGGATATGTCAACTACGATGTGGAATCAGACGGGAGAGTGAT
 GCGGATGAAACCAATTGAGATCCTTAGAGGCGATAAGAAAAGCAATTGAATTT
 CTTTCCTTTTTCAACACTTCTTAACCATGTTTCATCATTTTAATCTTTTCATTACA
 AAAACAAGGTCCTATTTTTTTTCTCGGGTACTACTCGCCTTTTCTAATAATTCA
 GAATCATCAATTTTTTGCCAACCTCTAGCTTTACATGTCTGTTTTTCATCATTTT
 CTCTCAAGCATTCTCCTAATATATTATGTTCCCTAGTATTTCCCCTCAGTCAGC
 AATTTTCTCGTCGTCGAAACCGTTTAGCTTTACTTTCAATCAAAACGTGGAAC
 ATTTTTCAAACTATTTGAAGCCAAAAAAACCAGGGCTTTTGTATATGTACCA
 TATTTTCCCTCTGATTTTCTTTATCGCCTTCTCTTTTCATGTAGAATAACTGAA
 ATACAAACCAATTTTAATTTTTTCTTTTAATTATCAATACTGTCCGTATAGGTAA
 AAATTATTTCTTCAGGTTTGAAAAAATCCGAAATATGTATCTGCAACTCTTCA
 GGGCATTGCCTCAATTAATTTTTATCTAATATTCAGATGGACCAACAAGAACC
 ATCGAATAACGTAGATACGAGCAGTATTCTTTCGGATGATGGGATGGAAACA
 CAGGAACAAAGTTCATTCGTCACCTGCTGTGAGTGAAATTATTTAAAATTTTCGC
 TTCGGAGATTCAATTGTCATATAATTCAATTTATCGATTTTCAGACAATTGACC
 TAACAGTGGACGACTACGATGAAACAGAAATACAGGAGATTCTGGATAATG
 GAAAAGCAGAAGAAGGAACAGATGAAGATTCTGATTTAGTTGAAGGGATTCT
 TAACGCTAATTCAGATGTCCAAGCGCTCCTTGATGCGCCATCTGAGCAAGTA
 GCTCAAGCTCTTAATTCGTTCTTCGGAAATGAGAGTGAACAAGAAGCTGTTG
 CAGCACAAAGACGGGTTGATGCGGAGAAGACTGCCAAAGATGAAGCTGAAC
 TCAAGCAACAGGAAGAGGCGGTTAGATTGGAATAAAGGAAGCAATAATAAA
 ATTATTTTATTTTCAGGAAGATCTTATTATAGAAGATTTCGATAGTCAAACTG
 ATGAAGAAAAACAAGCAGTTCGAAGACTGAAAATCAACGAATTTTATCGTG
 GTTCACAAGGCTCCTTCCAGAACAATTTAAAAATTTTCGAATTCACAAATCCGA
 ACTATCTGACAGAATCTATCAGCGATTACCGGTTGTAAATGTTCGATAAATGC
 AAGGAAATTGTCAAATCGTTCAAGGAAAGTGAATCACTTGAGGGACTTTCAC
 AGAAATACGAATTAATTGATGAAGACGTGCTAGTCGCTGCTATTTGTATTGGC

FIGURE 25

GTTCTCGATACCAACAACGAAGAAGATGTCGACTTTAATGTTCTATGTGATGA
TCGTATCGACGATTGGAGTATAGAAAAATGTGTCACCTTTCTTGATTATCCAA
ATACTGGATTGAATTTCGAAAAATGGACCGTTGAGATTCATGCAGTTTACTGTC
ACATCACCTGCATCAGCAATTCTCATGCTCACTCTGATTTCGATTACGCGAAGA
AGGGCATCCGTGTCGATTAGATTTTGATTCAAATCCGACTGATGATTTACTCT
TGAATTTTCGATCAAGTGGAATTTTCTAATAATATCATTGATACGGCAGTCAAA
TACTGGGATGATCAGAAGGAAAACGGTGCGCAGGATAAAATTGGCAGGCGA
GTATTAATCAAACCTCACAACCTGTTTTGAAAGTATTTTCATAATTATCACTTAA
ATACCTTTTAGAGAGCTCAACGACTTCTTCCACGAAATCGAGTCAACATCAGC
AGAATTCAAACAACATTTTGAGAACGCCGTTGGCAGCCGTAATGAAATAATT
CAACTTGTCAACGAGAAAAATCCCGATTTTGATGGCACTGAGGCTGCTGTGA
ATGAGAGTTTTACATCCGATCAACGAACCGAAATTATCAACTCTCGTGCAAT
AATGGAGACATTAAGCCGAGATGAAGCTCGCCATCGCCGAAGCTCAGAA
AGTTTACGACACCAAGACTGACTTCGAAAAATTTCTCGTTTTGACAGTTGGAG
ATTTCTGTCTGGCTCGCGCCAATCCTTCTGACGATGCAGAATTAACATACGCC
ATAGTTCAGGATCGTGTGGATGCAATGACCTATAAGGTTAAATTTATCGACA
CAAGTCAGATCAGAGAGTGTAACATCAGAGATTTAGCCATGACTACGCAGGG
AATGTATGACCCGAGTTTGAATACATTTGGTGATGTTGGTGAGTTTTAAGTTA
AAATTGATATTTAATATTACATCTGTTATGTAGAATAAGGGTTTCGGTTTTTC
GATTTTATTAGAAAAATCGAAAAATTTAGTTTTTGTGTTAAATTTAAAAAAATC
AAAATTTGATTCATATCAAGTCCGTTTTTCTCTTCTCAAAATTGACAAAATTT
TGATAATCTAGAATTTTTCGTCCCGTATATTTTCAACGAAAAACCATTTAAAA
TTTTCCATGATTGGATTTTTCGGTTGATCTAGAAAAAAATGGTGCTAAACACTA
AATTTGAAAAAGTTTGAACAAATTCAAATCCAAATATTTTCATGAAAACTT
GTAAAATATATTATGTACACAAAAAAACGTTTCAAGTGTAGCAGTTGTTTTTT
GTGGTCCCAAAAAAGCAGATGTTTGTGAGAATCCATTAAACAACAAAAAAAT
CCAAAAACTCAACCTGGCCTAGATATCAGTTTCATGATCGAAGTATCTAAAA
TCATTGTTTTCAGGTCTTCGAGTTGCCTGTGCGCAAGTTATTTCTCGAGCCAA
TTTGAAAAAAAACAATTTGGCTTACCGGTACAGCTGCCGGACGTGCGCAGAG
CTCATAGATCCGATTTTCTAATTTTCTTCGACAACCGGAACCGATGCATACGTG
TCAGCTCCGACAATGCCTGGTGAACCAGGTTATGAAGTTGCTTCTGAAAAGA
AAAGTGTATTTTCTCTCAAAGAAATGATTGCGAAGATGAATGCTGCTCAGATT
GCTATTATGGTTGGACAGCCAGTAGGAAAGGAAGGAAATCTGGATTATTTTT
TGACATTTTCATTGGATTTCGACAATCTCACAGATCAGCGTATATTCGGGATTTT
ATGAAAGAATTTCCGGAATGGCCACTTCTCAAGATGCCAGTTGGAATGCGAA
TCTGTTTGTACAATTCTCTTGTGATCGACGTAAGAAAAATGGTGACAGTGATT
GGAAGTATCGAGCTTTTGCTATTGTGAGACACGAAGCACCGAATCCATTGG
CTCCTGGGAATAGATGTACAGACTTCCGTGCAATGATAGAAATCATCAGCA
TATTGACGAGAAAAATCTATAGAGGATCTCATAGATTGGAAGGCGCAGCGGTA
AGATTTTATTTGAAAAATTGATACAAAACGAGGATTTTCTAAAATTATTTTAT
TTTTATTGATTTGATTTCTTATAATTGATAATCAAGGTTTTTTGGATGTTTTG
TTAGAGAAATCGAAAAGGGAACTTCCAAAAAAAAGCTGTGAAATCAATTTT
TGCTTTTAATAATATCCAAGTTTCATCTTCAAAGTTTTTTCTATAAAATGGACA
CAAACCTTTCAACGTTTTTCAAAAAAAAGGTTCCGAAAATATGAAAAAGGAG
AAAGAAATCATGAAAATTTTGTATTATTTTCAGCACAGAAGCACATGATCTC
GACAAATAACAATCTGTCGCAACGCAGAAAAGACCAGCTTCAATCACAGTTC
GAGCCAACCGACATGATTTCGTTTCGATGCCAGAGAGGAATCACCAACAAGTCG
TAAAAAGAAAACGACGGGCACCAATCAGAATGTCGCTTCGACAAATGATGC

78/92

FIGURE 25

AAAATCGAAGAGAGAAATTGAAATAAGAAAGAAAAATCAATTCTTATTTAAC
AAGATTATTGTTCCAATACCCGTCCTAACACCATTGGAAAATCTCAAGGCTCA
TGCTCAATGTGGTCCAGATTGTCTACAGAAAATGGATGCGGATCCGTATGAA
GCAAGATTCCATCGAAATTCACCAATACATACTCCTCTTTTGTGTGGTTGGAG
ACGAATTATGTACACAATGAGTACTGGAAAGAAGCGGGGAGCAGTGAAGAA
AAACATTATTTACTTTTCTCCATGCGGAGCCGCTCTTCACCAGATCAGCGACG
TCTCTGAATATATTCATGTCACCAGAAGTTTATTGACGATTGATTGTTTTTCAT
TTGATGCACGAATCGATACTGCCACTTATATTACTGTTGACGATAAATATTTG
AAGGTTGCTGATTTTTTCGCTTGGAACCGAAGGAATCCCAATTCCACTAGTGAA
CAGCGTGGATAACGATGAGCCTCCATCATTGGAATATTCGAAACGACGATTC
CAATACAATGATCAAGTGGATATATCGAGTGTTAGCCGAGATTTCTGTTCTGG
ATGCTCTTGTGATGGTGATTGCAGTGACGCATCGAAGTGTGAATGCCAACAA
TTGTCCATTGAAGCAATGAAACGACTCCCCATAATTTACAATTCGACGGAC
ACGACGAATTGTATGAGAGTTTCAAGAAAACAAAATAAATTTTTTAAACTATT
TTTTTTCAGAGTTTCTCACTATCAAAATCGTCTTCTCAGCAGTAAGGTTATCA
GTGGACTCTATGAATGCAACGATCAGTGTTTCATGCCATCGAAAGTCTTGTTAC
AACAGAGTTGTTTCAAGACAATATCAAGTATCCTATGCATGTGAGTTTATTTAA
CGATGATACATAACCAATTATTGTTTTTCTTCAGATCTTCAAACTGCTCAATC
CGGATGGGGAGTCCGAGCTTTGACGGATATTCCTCAAAGTACGTTCAATTTGCA
CGTATGTAGGTGCTATACTGACGGATGATTTGGCTGATGAACTAAGAAATGC
GGATCAATACTTCGCTGATTTGGACTTGAAGGATACCGTGGAGCTGGAAAAG
GGTCGCGAAGATCATGAACTGATTTTGGTTACGGAGGAGACGAGTCAGATT
ATGATGACGAAGAAGGAAGTGATGGTGACTCCGGTGATGATGTAATGAACA
AAATGGTGAAACGTCAAGACTCTTCGGAGAGTGGTGAAGAAACAAAACGGC
TGACAAGACAGAAAAGAAAGCAATCTAAAAAATCCGGTAAAGGAGGAAGTG
TGGAGAAAGATGACACCACTCCAAGAGATTCAATGGAAAAGGATAATATTG
AAAGTAAAGACGAACCCGTTTTCAATTGGGATAAGTATTTTGAGCCGTTTTCCA
TTGTATGTTATAGATGCAAAACAGAGAGGAAATCTTGGAAGGTAAGATCACA
ATTTTATTCATTAAAAAAATTTTTAGAGATTTTGCTTTAAATGATAAAAAAT
GGACAAACCAACCGTTTTGCCTCTTCTTTTGGTTTATCAACCTTTCTCTATGGAA
AAAATTCTGAAAAATTAACAAACAGTATTTACGTTGAAAAGTGAAGAAAAA
AGCAAAAAAAGGAAACAAATTTCAAAACGGTTCTACTCCATCTTAAAAAAAC
TAAATTCGTAAAAAGTCATTTGGTATGTTTTGGAGACTATAATACAATTGAG
AAAATTTGAAAAACCGGCACTCCAAGATACAATCATAAATTTTCGATAACT
TTCAGATTCTTGAATCACTCTTGCGATCCGAATGTGCACGTTCAACACGTCAT
GTACGATACGCATGATCTTCGTCTTCCATGGGTGCGGTTTTTCACACGAAAAT
ACGTGAAAGCCGGCGATGAGCTAACCTGGGACTATCAATATACTCAAGATCA
GACGGCTACCAACAACCTACATGCCACTGCGGAGCTGAAAACCTGCACCGGC
CGTTTGCTGAAAAGTTAAAGAATTGTTGTTATTTCCCTTCCCAGTTATGTTTTCC
TTTTTTTTTAAGTATTTATTTATTTAATTTTTATTTTGTATTGTTCAATC
GTTTAAAATCTCCCTTTGAAAACAGCATCTCATATGTATGATCTAAACACGTA
TTTACCTCGTAAGGGTTTGCCAAATAGTTTCTTTGGTTTTTCATTTTGATTTTCT
CTGCGAATAAAATGTTTTAAAAAAGACATTATTTTTTTAATAGTCAGTACAG
TTTTGATGTCTCCAATCTATTTTCAAGTTTACAATTTTAAAATATAGAATATATAT
ATTTAGGTTTCATAAGTTATGCATCGATTACGGGTTCTACGTCACCTTGAAGTT
CTGCATTTCCACGTCACATAGGACTACTGTAGTTTTTAAAAAATACTCGTTCAT
TTTGTAATAATATTCCTTCTACTAGTTTTGCTTCTGGTAATAATCGAATTTCAA
AACTTTAGCTAAAATATTTCTTTTTGAAGAGGCTGCAGCAAAATATGAAAAG

FIGURE 25

AAAAGTCCAACTGAACATGTATTACTTCGACCCGATACATATATTGGAGGTG
TCGCCATGCGAGAAGATCAAATTATTTGGCTCAGAGACTCAGAAAATAGAAA
AATGATTGCAAAAGAAGTCACTTATCCACCTGGATTATTGAAGATTTTCGATG
AGATTCTAGTGAATGCGGCTGATAATAAAGCAAGAGATTCCAGTATGAATCG
GTTGGAAGTATGGTTAGATAGGTAAATATATTGCAGGAATTTATGTTCTGCGA
CAAAGCTACGATACGCTGTCTCGCCACGACAATTGTTTTGGTAAATGCATGA
AAATCGACGTGCACCTTTAAATAATACTGTAGTTTTAAATTCTCGTTTCTTCA
ATTTTTCATAAATGGTTTTCCGATGAATATATGATTTTAAAAAATCTAAAT
TCACATTAATTTATAAGAAACAAAATTCCTCAAAAACGAAAGTTTGGCGATA
CAGTACTATC

Figure 26

LIN(n4256) amino acid sequence

MDQQEPSNNVDTSSILSDDGMETQEQSSFVTATIDLTVDDYDETEIQEILDNGKA
EEGTDESDSLVEGILNANS DVQALLDAPSEQVAQALNSFFGNESEQEAVAAQRR
VDAEKTAKDEAELKQQEEAEDLIIEDSIVKTDEEKQAVRRLKINEFLSWFTRLLPE
QFKNFEFTNPNYLTESISDSPVNVNDKCKEIVKSFKESSESLEGLSQKYELIDEDVL
VAAICIGVLDTNNEEDVDFNVLCDDRIDDWSIEKCVTFLDYPNTGLNSKNGPLRF
MQFTVTSPASAILMLTLRLREEGHPCRLDFDSNPTDDLLNFDQVEFSNNIIDTA
VKYWDDQKENGAAQDKIGRRVLIKLTTLVKNVAVGSRNEIIQLVNEKIPDFDGTGA
AVNESFTSDQRTEIINSRAIMETLKAEMKLAIAEAQKVYDTKTDFEKFVLTVDG
FCLARANPSDDAELTYAIVQDRVDAMTYKVKFIDTSQIRECNIRDLAMTTQGM
DPSLNTFGDVGLRVACRQVISSSQFGKKTITWLTGTAAGRRAHRSDFLIFFDNGT
DAYVSAPTMPGEPGYEVASEKKS VFSLEKEMI AKMNAQAIAIMVGQPVGKEGNL
DYFLT FHWIRQSHRSAYIRDFMKEFPEWPLLKMPVGMRICLYNSLVDRRKKMVT
VIGTDRAFAIVRHEAPNPLAPGNRCTDFPCNDRNHQHIDEKIYRGSHRLEGAAHK
KHMISTNNNLSQRRKDQLQSQFEPTDMIRSMERNHQQVVKKKTTGTNQNVAS
TNDAKSKREIEIRKKNQFLFNKIIVPIPVLTPLENLKAHAQCGPDCLQKMDADPYE
ARFHRNSPIHTPLLCGWRRIMYTMSTGKKRGAVKKNIIYFSPCGAALHQISDVSE
YIHVTRSLLTIDCFSFDARIDTATYITVDDKYLKVADFSLGTEGIPIPLVNSVDNDE
PPSLEYSKRRFQYNDQVDISSVSRDFCSGCSCDGDSCDASKCECQQLSIEAMKRL
PHNLQFDGHDELYESSEKQNKFLKLFFFRVPHYQNRLLSSKVISGLYECNDQCSC
HRKSCYNRVVQNNIKYPMHVSLEFNDDTYQLLFFLQIFKTAQSGWGVRAITDIPQ
STFICTYVGAILTDDLADLRNADQYFADLDLKD TVELEKGREDHETDFGYGGD
ESDYDDEEGSDGSDGDDVMNKMVKRQDSSESGETKRLTRQKRKQSKKSGKG
GSVEKDDTTPRDSMEKDNIESKDEPVFNWDKYFEPFPLYVIDAKQRGNLGRFLN
HSCDPNVHVQHVMYDTHDLRLPWVAFTRKYVKAGDELTWDYQYTQDQTATT
QLTCHCGAENCTGRLLKS

Figure 27

lin-65 genomic sequence (1 kb of upstream and downstream genomic sequence is included in this file)

<u>Exon number</u>	<u>Exon boundaries (inclusive)</u>
1	1001 – 1133
2	4522 – 5208
3	6128 – 6361
4	7962 – 8350
5	8706 – 8928
6	9260 – 9516
7	10328 – 10567
8	11677 – 11700

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AAAAATTTAAAAAAATTTTTAAAAATTCGTGTAAAAATTACCCCGGTTGTTTA
GGAAATAATAAAGAGATTAGAGACTTTTTTCAGATTTTATTTTCTTGAGTTT
TGCCGGTTTTTCAGCCGATTTCTATCTTTTTTTTCTCATTTTTTGTGATTTTTTT
CGCTAGTTTTCCCTCAATTTCTCGATTTTTTCACGATTTTTTGAAAATTTTCG
GAAAATTGAATTGTTTGCAAAAAAAAAAAATTCAAAAACCGCATTTTTCTCAG
AATTTTTCTGGGATTTTGTACAAATTTTGAATTATTTCTCAAAAAAAAAAGCAG
GTTTTTACCGATTTTTTTGGTTTTTCCCCAAAATTTTCCGATTTTTTCCGAGTT
TTGCCGGTTTTTCAGCCGAATTCTACTCTCGATTTTTTTTACGATTTTTTGGAAAT
TTTCGGAAAATTATTTGAAAAAAAAATCAAAAACCGCATTTTTTTTTCTGAAT
TTTCTGGGATTTTGTACGAAATTTTGAAATTTTTCTCGAAAAAAGCAAGTTAT
TCCCCAAAATTTTCTGATTTTCCCCCAAAAATTTAGATTTTTTCCCGAGTTTTCC
CCAGTTCTCAGCTGATTTCTATATTTTTTTTCTCAATTTTTGTGATTTTTTGTGTC
TAGTTTTCCCTTCAATTCCTCGAGTTTTTCACGATTTTTTGGAGATTTTCGAAA
AATTGTTTGAAAAAAATCAAGAAACCACATTTTTTCTCTGGATTTTCTCGAAAT
TTGCACAAAATTTTTGAATTTTTTCGTAAAAAAAACGTGTTTTCCCCAAAAT
TTCAGATTTGTTTTTGATTTTTTTTCGAGATTTTCCCTGATTTCAAAGTTTTTTC
CTGAATTTTTTCGAATATTTTCTGAAAAATCGGCTATTTCTAACTTTTTAAATAA
TTTTTTTTGAATTTCTGACTTTTTTAAATCCTTTTTTTTTTTGCCATTTTTTCCCATC
TAAATTTCTAAATTATTCAAAATTTTACAGAATGTCAGAAGTAATCGACGAA
AGTATCTTAAATACAGAAGCTTCAGATGATCCAATACCTCCATTAAATGATG
ATCAGATTGCTGAGCTTTTGGGTGAAGATGGAGAAATTATGGAGATAACTGA
GCAGAAAGGTGAGATTTTTTGAGTAAAACCTTGAATTTTGCCTAAAAATTTG
CAATTTTTCGCTAAAAATTACCTTAAAACTCGAAAATTGGAATTTCTAGCTGAG
AAAATGGCCAAAAATGTCGAAAAATGCCTCCGAAACCTGTGAAAAAAAAAAAA
CCACCAAAAAGGTTTCTAGGCCACCAAAAAGATTTCTAGGCCACCAAAAATG
TTTCTAGGCCACCAAAAATGTTTCTAGGCCACCAAAAATGTTTCTAGGCCACC
AAAAATGTTTCTAGGCCACCAAAAATGTTTCTAGGCCACCAAAACAGGTTTCA
ATGCCACCAAAAATGTTTCTAGGCCACCAAAAATGTTTCTAGGCCCCCAAAA
AATTTTTCTAGGCCACCAAAAAGGTTTCTAGGCCACCAAAAATGTTTCTAGGC
CACCAAAAAGGTTTCTAGGCCACCAAAACAGGTTTCAATGCCACCAAAAAGGT
TTCTAGGCCACCAACCAGGTTTCAATGCCACCAAAAATGTTTCTAGGCCACCA
AAAAGGTTTCTAGGCCACCAAAAATGTTTCTAGGCCACCAAAAATGTTTCTA

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FIGURE 27

GGCCACCAAAAAGGTTTCTAGGCCACCAAAACAGGTTTCAATGCCACCAAAAA
TGTTTCTAGGCCACCAAAACAGGTTTCAATGCCACCAAAAAGGTTTCTAGGCC
ACCAAAAAGGTTTCTAGGCCACCAAAAATGTTTCTAGGCCACCAAAAAGGTT
TCTAGGCCACCAAAACAGGTTTCAATGCCACCAAAAATGTTTCTAGGCCACCA
AACAGGTTTCAATGCCACCAAAAATGTTTCTAGGCCACCAAAACAGGTTTCAA
TGCCACCAAAAATGTTTCTAGGCCACCAAAAAGGTTTCTAGGCCACCAAAA
TGTTTCTAGGCCACCAAAAATGTTTCTAGGCCACCAAAAAGGTTTCTAGGCCA
CCAAACAGGTTTCAATGCCACCAAAAATGTTTCTAGGCCACCAAAACAGGTTT
CAATGCCACCAAAAATGTTTCTAGGCCACCAAAAATGTTTCTAGGCCCCCAA
AAAATTTTCTAGGCCACCAAAAAGGTTTCTAGGCCACCAAAAATGTTTCTAG
GCCACCAAAAAGGTTTCTAGGCCACCAAAACAGGTTTCAATGCCACCAAAAAG
GTTTCTAGGCCACCAACCAGGTTTCAATGCCACCAAAAATGTTTCTAGGCCAC
CAAAAAGGTTTCTAGGCCACCAAAAATGTTTCTAGGCCACCAAAAATGTTTCT
TAGGCCACCAAAAAGGTTTCTAGGCCACCAAAAAGGTTTCAAGGCCACCAAAA
AAGGTTTCAATGCCACCAAAAATGTTTCTAGGCCACCAAAACAGGTTTCAATG
CCACCAAAAAGGTTTCTAGGCCACCAAAAATGTTTCTAGACCACCAAAAAGG
TTTCTAGGCCACCAAAACAGGTTTCAATGCCACCAAAAAGGTTTCTAGGCCAC
CAAACAGGTTTCAATGCCACCAAAAATGTTTCTAGGCCACCAAAAAGGTTTCT
TAGGCCACCAAAAATGTTTCTAGGCCACCAAAAATGTTTCTAGGCCACCAAAA
AAGGTTTCTAGGCCACCAAAACAGGTTTCAATGCCACCAAAAATGTTTCTAGG
CCACCAAAACAGGTTTCAATGCCCCCAAAAATTTTCTAGGCCACCAAAAAG
GTTTCTAGGCCATCAAAAATGTTTCTAGACCACCAAAAAGGTTTCTAGGCCAC
CAAAAATGTTTCTAGACCACCAAAAAGGTTTCTAGGCCACCAAAAATGTTTCT
TAGGCCACCAAAAAGGTTTCTAGGCCACCAAAAATGTTTCTAGGCCACCAAAA
AAGGTTTCTAGGCCACCAAAACAGGTTTCAATGCCACCAAAAAGGTTTCTAGG
CCACCAACCAGGTTTCAATGCCACCAAAAATGTTTCTAGGCCACCAAAAAGG
TTTCTAGGCCACCAAAAATGTTTCTAGGCCACCAAAAATGTTTCTAGGCCACC
AAAAAGGTTTCTAGGCCACCAAAAAGGTTTCAAGGCCACCAAAAAGGTTTCA
ATGCCACCAAAAATGTTTCTAGGCCACCAAAACAGGTTTCAATGCCACCAAAA
AGGTTTCTAGGCCACCAAAACAGGTTTCAATGCCACCAAAAAGGTTTCTAGAC
CACCAAAAAGGTTTCTAGGCCACCAAAACAGGTTTCAATGCCACCAAAAAGGT
TTCTAGGCCACCAAAACAGGTTTCAATGCCACCAAAAATGTTTCTAGGCCACC
AAAAAGGTTTCTAGGCCACCAAAAATGTTTCTAGGCCACCAAAAATGTTTCT
AGGCCACCAAAAAGGTTTCTAGGCCACCAAAACAGGTTTCAATGCCACCAAAA
ATGTTTCTAGGCCACCAAAACAGGTTTCAATGCCCCCAAAAATTTTCTAGGC
CACCAAAAAGGTTTCTAGGCCACCAAAAATGTTTCTAGACCACCAAAAAGGT
TTCTAGGCCACCAAAAATGTTTCTAGACCACCAAAAAGGTTTCTAGGCCACC
AAAAATGTTTCTAGGCCACCAAAAAGGTTTCTAGGCCACCAAAACAGGTTTCA
ATGCCACCAAAAATGTTTCTAGGCCACCAAAAATGTTTCTAGGCCCCCAAAA
AATTTTCTAGGCCACCAAAAAGGTTTCAATGCCACCAAAAATGTTTCTAGGC
CACCAAAAAGGTTTCTAGGCCACCAAAAATGTTTCTAGGCCACCAAAAATGT
TTCTAGGCCACCAAAAAGGTTTCTAGGCCACCAAAACAGGTTTCAATGCCACC
AAAAATGTTTCTAGGCCACCAAAACAGGTTTCAATGCCACCAAAAAGGTTTCT
AGGCCACCAAAAATGTTTCTAGACCACCAAAAAGGTTTCTAGGCCACCAAAAC
AGGTTTCAATGCCACCAAAAAGGTTTCTAGGCCACCAAAACAGGTTTCAATGC
CACCAAAAATGTTTCTAGGCCACCAAAAAGGTTTCTAGGCCACCAAAAATGT
TTCTAGGCCACCAAAAATGTTTCTAGGCCACCAAAAAGGTTTCTAGGCCACC
AAACAGGTTTCAATGCCACCAAAAATGTTTCTAGGCCACCAAAACAGGTTTCA

ATGCCACCAAAAATGTTTCTAGGCCACCAAAAATGTTTCTAGGCCCCCAAAA
AATTTTTCTAGGCCACCAAAAAGGTTTCTAGGCCACCAAAAATGTTTCTAGAC
CACCAAAAAGGTTTCTAGGCCACCAAAAATGTTTCTAGACCACCAAAAAGGT
TTCTAGGCCACCAAAAATGTTTCTAGGCCACCAAAAAGGTTTCTAGGCCACC
AAAAATGCTTCTAGGCCACCAAAAATGTTTCTACGCCACCAAAAAGCCGCCTC
AAGCCCGAAAAATTTGAATTTCCCGCTCAAAAAATCTAAAATTTTCCGATTTT
CAGACGAATCAGATGATGTGGTGATGCTGGACGACGATGATGACGACACTCC
GGAACCGATTCTCGTGATTGATATGGATGAGGATGAGGATGTTACTACAGAT
GGTCCTGAATCTCAGGAAGAGCTGGCTGCAGATGCTCCGGCTCCAGGAGCTC
CAGAAGCTTCAGCTCCAGCTCAAGAAGCCTCAGAAGCTTCAGCTCCGGATCA
AGAAGCTCCAGAAGTTCAGGATGTTCCGGATTCTTCGGGAGCTCCAGATGCT
TCAGCTCAGGCTTCAGAGGCTTCTGATGCTTCAGCTCCAGAAGTTCAGGATC
TACAGAAGCTCAGGATGCTCAGGATGTTCCGGATTCTTTGGGAGCTTCAGAT
GCTTCAGCTCAAGAAATTCAGAAGCTCCAGAAGCCCCAGAAGCTCCAGAAA
TCGCCGCTGAAATCGACGAAGAAGTGCTGCTCGCCGAGCAAAATGGAGTTTT
GGACGAAGGATTTGATGAGACTGACGATATTATCATAGAAGAAGAAGCTGTA
GAAGAAGCTGAAGCCGTGGAGCCACCAATTAACACTGAAAATCAGGAAAAC
GCGCTGGAAATGCTCGAAGAGCGCCTCAAGAAGAATGAAGAAAAGGAAATT
GTGGAGAAAAGTGATGTGAAGCCAGAGGATGAAGATATTATACATATGGAG
ACGGATTCAGTTGAAAGTATGGGCTTTTTTAGCTGGAAAACAGGAAAAAAGA
GCAAAAAATTGATACATTTCCAGCTTAACCAATCTTTTTTTGAGTTGTAAAGC
CTGAAAATTGAGATTTTTGTACCAACTTTTATGATAAAGCTGAAAAAAAATT
AATTTTTTGACGAATTTTATAGCGGAAACCCTGAAAACATGTTTTGTCTGAAAA
ATACAGAAAATCGTCACTTTTTACAATAAATTCGAGATTTTTAGCTCAAAAAT
ACAACATTATAGTGCAAAAATCTCAGAAAAAGCCAAAAATTTCAATCAACA
TCTCAAAAAAAGCAGAAATTTTACTCAAAATATCTCAGAAAAAGCTAAAATT
TTCCCAAAAAATCCCAGAAAAAGCAGAATTTTCAATCAAAATTTCCAGAAAA
AGCTGATAATTTACTAAACAATCTCAGAAAATGCTGAAATTTTACTCAAAAG
TCTTCATAAAAAAGCTGAAATTTTACTTTAAAAGTTTAGGAAATGCTGCAATTT
CACTTAAAAATCCCAAAAAAGCTAAAATTTTCCCAAAAAATCCCAGAAAAAG
CAGAAATTTTACTCGAATATCTCAAAAAAAGCTGAAATTTCACTCAA
AAATCCCAGAAAAAGCTAAAAATTTACTAAAAAATCTCAAAAAAAGCG
CTAAAATTTCACTCAAAAATCTCAGAAAAAGCTAAAATTTTACTCGAATATCT
CAAAAAAAGCTGAAATTTTCTAAAAAATTTATGAAAAACCGAAATTTT
ACTTAAAAGTCTCATAAAAAGCCGAATTTTCCCAAAAAAATCCCAGAAAAAG
CTAAAATTTACTTTAAAATCTCATCTGTAATTTTAGTTTAAAATCTCAGAAA
AACCCGAAATTTCTCTCAAAAATTTGCTGATTTTCAAATTTTCAGCGTCAAGC
CGCAAACGTAAGTGGCGGAGCCACAAGTCCGCGGAGCCCGGCTCAAAAACGA
CCAAAACGACGTGTTCAAACGTTATTAAAGATGCGTCAGAATGCAATTGAAC
TATTGACACGACTTTATGGCTCATGGGATGCACAATTGAGCCTCTCAAATCTT
GAGACAATTCGATTGTTGGGTGTCAATAATAATAGGAAGCTTATCGAAATTTT
TGAGGAGAATGAGCAAGGTTAAAGCGTTTTTAAATGCTATGAAAACCTGACAA
ATTTTCGATAAAAAAAGCGATTTTGGGAAGAAAATCGCCTGAAAATTCATGT
TTTTCTGCAATTTTGACCAAATTTCCCAAGAAAAATACGATTTTTTAGTCCGA
AAATCCTCCAAAAAGATTTCTAGGCCACCAAAAAGGTTTCTAGGCCACCAAG
AAAGTTTCTAGGCCACCAAGTATTTATAGGCCACCTAAGATGTTTCTAGGCC
ACCTGAGATGTTTCTAGGTACCAAAAATGTTTCTCGGTACCAAAAATGTTT
CAAGGCCACCGAAAAGGTTTCTAGGCCACCTAAGTATTTCTAGGCCACCTAA

FIGURE 27

GATGTTTCTAGGCCACCTGAGATGTTTCTAGGTCACCAAAAATGTTTCTAGGT
TACCAAAAATGTTTCAAGGCCATCGAAAAGGTTTCTAGGCCACCAAAAGTATT
TCTAGGCCACCTAAGATGTTTCTAGGCCACCTGAGATGTTTCTAGGTCACCAA
AAATGTTTCAAGGCCACCGAAAAGGTTTCTAGGCCACCAAAAAGGTTTCTAG
GCCACCAAAAATATTTCTAGGCCACCTAAGATGTTTCTAGGCCACCTGAGAT
GTTTCTAGGCCACCTGAGATGTTTCTAGGCCACCTGAGATGTTTCTAGGTCAC
CAAAAATGTTTCTCGGTACCAAAAATGTTTCAAGGCCACCGAAAAGGTTTCT
TAGGCCACCTAAGTATTTCTAGGCCACCTAAGATGTTTCTAGGCCACCTGAGA
TGTTTCTAGGTCACCAAAAATGTTTCTAGGTTACCAAAAATGTTTCAAGGCCA
TCGAAAAGGTTTCTAGGCCACCAAAAGTATTTCTAGGCCACCTAAGATGTTTCT
AGGCCACCTGAGATGTTTCTAGGTCACCAAAAATGTTTCAAGGCCACCGAAA
AGGTTTCTAGGCCACCAAAAAGGTTTCTAGGCCACCAAAAATATTTCTAGGC
CACCAAAAATGTTTCTAGGTCACCAAAAATGTTTCTAGGTCACCAAAAATGT
ATCAAGGCCACCAAAAAGGTTTCTAGGTCACCAAAAATGTTTCTAGGCCACC
AAAATGTTTCTAGGTCACCAAAAATGTTTCTAGGCCACCAAAAAGGTTTCT
AGGCCACCAAAAAGGTTTCTAGGCCACCAAAAAGGTTTCTAGGCCACCAAAA
AGGTTTCAAGGCCACCAAAAAGGTTTCTAGGCCACCAAAAATGTTTCTAGGT
CACCAAAAATGTTTCTAGGCCACCAAAAGTATTTCTAGGCCACCTAAAAGGTTT
CTAGGCCATCAAAAAGGTTTCTAGGCCATCAAAAAGGATTCTAGGCCACCAA
AAATATTTCTAGGCCACCTAAGATGTTTCTAGGCCACCAGAGTATTTCTAGGC
CACCTAAGAGGTTTCTGGGCCATCAAAAAGGTTTCAAGTCCATCAAAAAGGT
TTCTAGGCCACCAAAAAGGTTTCTAGGCCACCGAAAAGGTTTCTAGGCCACC
AAAAGGTTTCTAGACCACCTAAGACATTTCTAGGCCAACAAAAAGGTTTCT
AGGCCACCAAGAAGCCGAAAACTGTCTCAAATTCGAATTTTGCAGTGCTCA
AACAAAAAGTGTCGCACTGACAGAAGAGCTGAAAAAGGAGAAGCTGGCTC
ACGCGGGAACCCGTTCAAGCATTGAAAGAATTGACTAATGAAATAACTGGAAT
GCGTGTAACAATGAATAAACTACGTTCAATGGTCACTCAGCCTACGACTTCG
AAAATTATTGATAGTTTTGTTCAACGTCAATCAGGCTTTCGAGCAGCAACAACA
ATTCCAACACCAACACCACCAACACCGACCAATAATGTTGGCTCCACGTCAT
CATCCGCCGCCGCCCGCATTTTACACCGAATCAACGGGCGGCGGCTCCGT
ATCATCCGAATATGGTTCAACCGAATCGTCTTGCTGCTATGCCACATAGAAGA
CCGATTATTGGAATGCAGGTGAAAATGGAATGCCATGAAAATTTCCGGGCCGG
AAAATTTTGGAATACTCTAAATTTTCAATATTTGTCGAAAAAATCTGACAA
AAATCGTGTCAAAATTCAGATTTCCGGGAGAAAAATCGCATTTTTGAGTAAA
AATTCGAAGAAAAGCGTCTTAAATTCTAGATTTATTAGTTAAAAATTTTTTCA
AATTTTAGTCAAGAAAATTAAGAAAAATGCGAAAATTTTCGAGCAAAAAATAT
AGTTTTTTGGAGCCGAAATTGTGAAAAATGCGATTTTTTTTCGAAAAATCTGGA
CAAAAATTTCAAACAAGAAAAACCCTTTTTTAAAAAAATTTTCACACAAT
TTCCAGCAACAAAATTCGGCTCCACCACAATTCAACGGTCACCAAGCTCTCGT
CCCATCACCTCAATCATCATCTGCATTTTCTCGTCCACCACCAACTCAACTTG
CAACACAGAGAAGAGCTCCACCATTGGCAAGTACCGGCCTTCCGGCAACAGT
CAGATGGGAAGCAATTCCACCGCCAAAAAATCCGAATGTCGGGCACAATGA
GCCACCGCTTAACAATGGAGGTTTCGTGCTGTGCAACAAAAAGAGCACCGCTT
TTCCACGACGAGTTTTTGGGATGATGATTTTGGTGTGAAAATTGAAAACTCA
TTTTTTTAAAGTCTGAAATTTGAAAATTTGAGAAAAGTTTTTTAAAAAAAGTT
TTATGAGGGATTTTCTGACAATTTTTTATAAACGGAAAATTACGAAAACCTCCA
AAATTTGTGTTCTTTTCGGAAAACGAATTTGAAATTTGAACCAAAAATTTTGACA
ATTTTCTGGGGATTTTTGACTGGAAATTCGTTTTTTCATCGATTTTTCTCCTTT

FIGURE 27

AATTTTCGGTAAAACCCCTGTCTCCAATTCCAGGCCGTGCACAGCCACTAATC
GATAATACACGTGTACACGACAATACAATTATGCTGTGTGTACCACTTGTCTC
CACTGCAAATACAATATCATCGGGCGATTTCGACACGTCTACCAAAAGTACCA
CGAATCTACGAGAATCTCACGGCAAATCCCGATTGAGTGTGACGATTCATTC
GAGTGCACAGGATTTCCGAGAGAATTATCAAATTGGTGGAAAGATTAAGTAT
GAATATCTCGGAGGATTTGATCAATATGTAGGTGATGATGTTTTTTTTATTGAG
AGATAAATACGAAATTCCATTACAATCGATATTTTTTGACTGAAAAATGTCTG
AAAAATCAAAAATTTTAGCTAAAAATTGAGAATATTTTTGTTTAAAAAAAT
CATTGAAATTGATTTTTTTTTATTCCATAAAAAATCTCGGAAAAGTCAATTTTC
AGTCATAAATCTTCTGAAAATTATCCAAACAATGGGATTTTCTGAAATTTTAG
CTTAAAAATTGAGGATTTCCCGGTTTTTTCAGAGAAATTCCATTACAATCGAT
TTTTTTACTGAAAAATCCTCTGGAAATTAACAAAAACCAAATAAAATGCCCT
AATTTTTTTTTTAAATCCAAAAATTGTTGGATTTTTTCAGAAAAAAATATTTTTT
CAATTGACTGGTGTCCAAAAATATAGAAAATTCAAATTTTCCAAGAAAAAT
AGCCAAAAAAATGTAATTTTTGTCTAACAAAAAAATTGAATAGCGCAAAAT
AAATTGTCGTTTTTTTTAATTTCCCTCCGGTTTTGAAAGGAAAAAATTCCATA
AAAATCGAAATTTTTTGACTGAAAAATCCATGAAAATCGAATTTTGAGTCA
AAAATCCTCTGAAAATGCTCCAAAAATATGAGATTTTCTGAAATTCATCAAAA
ATTAAGAATTTACGGTTTAAAAAAATTCATTAAAATCGATATTTTTCAAG
TGAAAAATCTCTGGAAAATCGATGTTTGAGTCAAAATTCGTCTGAAAATGC
TCCTTTAAATTGAAAAATTGAAAAAAAACCGCCACAATATTTGCAGAATA
TCCAAGTGTTTCGTCCAAGTGTCATCTCTTAAATTCAGTGAATGAACGGTTAC
CCGGATCCAGAAGATCGTATATCAATTGACTGGGGATGCTCGAAATTGTGGC
CTTGTAAGCCGAAATCTCATCAAAATTCGGTGTACGCTTCCATCAAGCACAA
CTGCTGCCGAAGAACGATCGAATTACGATTGTGGCTGTGGCGAAGGATAAAA
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TATCTGAAATTTTCAGCAAAAAAATGAAAAAATAATCCGAAATTAATA
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TTTGCTAACCATTTGAGAATATTACGATTTTGTGAAAAAATAACCATTAATA
TTGATTTTTTATTCCTAAAAAATGCCAGAAAAATCAATTTTCAGTCAAAAATC
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CAATTTTCATTCAAAAATCCCCCGGAAAATTGTCAAAATTTTGAGATTTT
CTGAAATTTACGCAAAAAATTTTCATTTTTTCAGCCACCTTCATCACTCTCGA
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FIGURE 27

ATTTGAAATTCTCGTGTTTTTCTTCTGAAAAATTGCTTTTTTTGATTTTTCTG
TAATTTTTTTTTTGTGATTTTCTTAATTTTTTAATTTTCAAAAAATCTTTTC
ATCTCTTCTCTCTCTCTGAATCTCAATTTTTCTGAATTTCCCCGTTTTT
TCTGATAATTTCAATATTTCTCTGAATTTTCTATTCCCCCGTTGTAATGCC
AAAATATGTGGTAATTTCTCCCATTTTTTCGCTTTATTACTATTTATTCTATT
CAATTGGTGCCTCTCTCAATGTGTTGTATGAAAAACACTGTTTTATGGAGGTT
TTGGAGAATTTTGAATTTTTTCGTCTGTGATTTTTATTGGTTTTCTTTACCAATT
CAATTTTTTTTTTAATTCGAAAATTTGTAGAAATTCACTTTTGTAGCTTAAAAA
ATTAAAAATTGAGAAAATTTGTTCAAAAATGGCAAAGTTTTCGAAATTTTAGT
CTAAAAAAAGATTTTTTTAATATAGAATTTTAAAAAATTAGCACAGAAAAAT
GCCGAAAAATTCGTAATTTTTTCATTTAAAAATGAAAAAAAAAAAAACAAAA
AAAAAAAAAAAAAGAGGGAAAAATCCCATTAAGTAGTTTTTTGACTGC
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GATTTTTTTCCGATTTTTTCAAAAAATCCCCCTTCTAAAAAAATGGTGAAT
TTGTTCCCAAAAACCAAAAATTTGAGATTTTCTAAAATTTTGGCAAAAATTAA
GAATTTACGGTTTTTGAGAGGGAAAACTCCATTAAAATTGATGATTTTATGA
CTAAAAATTCCTAAAAAATCAATTTTCAGTCAAAAATTAAATTT

Figure 28

MSEVIDESILNTEASDDPIPLNDDQIAELLGEDGEIMEITEQKDESDDVVMLDDD
DDDTPEPILVIDMDEDEDVTTDGPESQEELAADAPAPGAPEASAPAEASEASAP
DQEAPEVQDVPDSSGAPDASQAASEASDASAPEVPGSTEAQDAQDVPDSLGLASD
ASAQEPEAPEAPEAPEIAAEIDEEVLLAEQNGVLDEGFDETDDIIIEEAVEEA
VEPPINTENQENALEMLEERLKKNEEKEIVEKSDVKPEDEDIHHMETDSVETSSRK
RTGGATSPRSPAQKRPKRRVQTLLKMRQNAIELLTRLYGSWDAQLSLSNLETIRL
LGVNNNRKLIIEFEENEQVLKQKVSALTEELKKEKLAHAGTRSALKELTNEITGM
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VPSPQSSSAFSRPPPTQLATQRRAPPLASTGLPATVRWEAIPPKNPVGHNEPPL
NNGGRAQPLIDNTRVHDNTIMLCVPLVSTANTISSGDSTRLPKVPRIYENLTANPD
LSVTIHSSAQDFRENYQIGGKINYEYLGGFQYNIQVFVQVSSLKFTGMNGYPDP
EDRISIDWGCSKLWPCKPKSHHKFRVRFHQAQLLPKNDRITIVAVAKDKTSGIHI
SQPTFITLE

Figure 29

```

1  aaggaattag actctttatc taaagtgaag aatgatcaat taagaagttt ttgtcccata
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121 aaaactgatg ctgttttaat gacttctgat gatagtgtga ctggatcggg attatcccct
181 ttgggtcaaaag catgcatgct ttcatacaaat ggatttcaga atattagtag gtgcaaagaa
241 aaagacttgg atgatacctg catgctgcat aagaagtcag aaagcccatt tagagaaaca
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481 gaaaaatattg agccttcagt tatgaagatt tcttcaaata gctttatgaa tgtgcatttg
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661 ttatatcaac ctattgggag ttcaggtatt gcttcatctc ttcagagtct tccaccagga
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841 gtagaagtat gtagtgacct tcctgattca ggaaaaggat ttgcttccag ggagaaacagg
901 cgtaataatg ggttatctgg gaaatgtttg caagaggctc aagaagaagg gaattccata
961 ttgcttgaaa gaagaggaag accagaaatc tcttttagat aaagaggaga aggaggacat
1021 gtgcatactt ctgatgactc agaagttgta ttttcttctt gtgatttgaa ttaaccatg
1081 gaagacagtg atgggtgaac ttatgcatta aagtgtgaca gtagtggtca tgccccagaa
1141 attgtgtcta cagttcatga agattattct ggctcttctg aaagttcaaa tgatgaaagt
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1261 gtgggtgtgc caaagaattc tactttgccc atggaagaaa caagtccttg ttcttctcgg
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1381 agacatttgt atgaggaaaa atttgaaagt atagcaagta aagcctgtcc tcaaaactgat
1441 aagtttttcc ttcataaagg aacagagaag aatccggaaa tttcttttac acagtccagt
1501 agaaaaaaaa tagataaccg cctgcctgaa ctttctcatc ctccagagtga tgggggttgat
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1621 gtgaaagcca aaataccttc taggcagcaa gaagagctgc caatttatte ttctgatttt
1681 gaagatgtcc caaataagtc ttggcaacag accactttcc aaaacaggcc agatagtaga
1741 ctgggaaaaa cagaattgag tttttcttcc tcttgtgaga taccacatgt ggatggcttg
1801 cactcatcag aagagctcag aaacttaggt tgggacttct ctcaagaaaa gccttctacc
1861 acgtatcagc aacctgacag tagctatgga gcttgtggtg gacacaagta tcagcaaaat
1921 gcagaacagt atgggtggac acgtgattac tggcaaggca atgggtactg ggatccaaga
1981 tcaggtagac ctcttggaa cgggggttg tggatcgaa ctcaaggca agtaccagat
2041 tccctaacag atgactgtga agaagaggag aattgggatc aacaggatgg atcccatttt
2101 tcagaccagt ccgataaatt tcttctatcc cttcagaaag acaaggggtc agtgcaagca
2161 cctgaaataa gcagcaattc cattaaggac actttagctg tgaatgaaaa gaaagatttt
2221 tcaaaaaact tagaaaaaaa tgatatcaaa gatagagggc ctcttaaaaa aaggaggcag
2281 gaaatagaga gtgattctga aagtgatggg gagcttcagg acagaaagaa agttagagtg
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2521 tctcatcgag atattaagcg aatgcagtgt gagtgtacac ctctttctaa agatgaaaga
2581 gctcaagggtg aaatagcatg tggggaagat tgtcttaatc gtcttctcat gattgaatgt
2641 tcttctcggg gtccaaatgg ggattattgt tccaatagac ggtttcagag aaaacagcat
2701 gcagatgtgg aagtcatact cacagaaaag aaaggctggg gcttgagagc tgccaaagac
2761 cttccttcga acacctttgt cctagaatat tgtggagagg tactcgatca taaagagttt
2821 aaagctcga tgaaggagta tgcacgaaac aaaaacatcc attactattt catggccctg
2881 aagaatgatg agataataga tgccactcaa aaaggaaatt gctctcggtt catgaatcac
2941 agctgtgaac caaattgtga aacccaaaaa tggactgtga acggacaact gaggggtggg
3001 tttttacca ccaaactggt tccttcaggc tcagagttaa cgtttgacta tcagttccag
3061 agatatggaa aagaagccca gaaatgtttc tgcggatcag ccaattgccg ggggttacctg
3121 ggaggagaaa acagagtcag catcagagca gcaggaggga aaatgaagaa ggaacgatct
3181 cgtaagaagg attcagtgga tggagagcta gaagctctga tggaaaatgg tgagggtctc
3241 tctgataaaa accagggtgct cagcttatcc cggctaattg ttagaattga aactttggag

```

FIGURE 29

```

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3541 actaagactg ctgtccctcc gttgagtga ggagatgggt attctagtga gaatacatcg
3601 cgtgctcata caccactcaa cacacctgat ccttccacca agctgagcac agaagctgac
3661 acagacactc ccaagaaaact aatgtttcgc agactgaaaa ttataagtga aaatagcatg
3721 gacagtgcaa tctctgatgc aaccagtga ctagaaggca aggatggcaa agaggatctt
3781 gatcaattag aaaatgtccc tgtagaggaa gaggaagaat tgcagtcaca acagctactc
3841 ccacaacagc tgcctgaatg caaagttgat agtgaaacca acatagaagc tagtaagcta
3901 cctacatctg aaccagaagc tgacgctgaa atagagctca aagagagcaa cggcacaaaa
3961 ctagaagaac ctattaatga agaaacacca tcccaagatg aagaggaggg tgtgtctgat
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4141 caaactgaaa aggaaaacac aacaactgaa cgaggaggg atgctgttgg tctcagagat
4201 caaacactg cccgaagac tcctaatagg tcaagagaga gagaccaga caagaaaact
4261 caaaataaag agaaaaggaa acgaagaagc tccctctcac caccctcttc tgcctatgag
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4561 ggttatccca tgcaggccta tgtggatccc agcaacccta atgctggaaa ggtgctcctg
4621 cccacacca gcatggaccc agtgtgttct cctgctcctt atgatcatgc tcagcccttg
4681 gtgggacatt ctacagaacc cctttctgcc cctccaccag taccagtggg gccacatgtg
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6061 acccatgcgc atccccacce acaacctttt accctgatga tctgtattat attttaatgt
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6361 ttttctctga actttttatg taaaaaata aaatcaatta aag

```

Figure 30

KELDSLKVKNDQLRSFCPIELNINGSPGAESDLATFCTSKTDAVLMTSDDSVTGSELSPLVKACMLSSNG
FQNI SRCKEKLDDTCMLHKKSESPFRETEPLVSPHQDKLMSMPVMTVDYSKTVVKEPVDTRVSCCKTKDS
DIYCTLNDSNPSLCNSEAENIEPSVMKISSNSFMNVHLESKPVICDSRNLTDHSKFACEEYKQSIGSTSSA
SVNHFDLYQPIGSSGIASSLQSLPPGIKVDSLTLKCGENTSPVLDAVLKSKKSSEFLKHAGKETIVEVG
SDLPDSGKGFASRENRRNNGLSGKCLQEAQEEGNSILPERRGRPEISLDERGEGGHVHTSDDSEVVFSSCD
LNLTMEDSDGVTYALKCDSSGHAPEIVSTVHEDYSGSSESSNDESDSEDTSDDSSI PRNRLQSVVVVVPN
STLPMEETSPCSSRSSQSYRHYS DHWEDERLESRRHLYEEKFESIASKACPQTDKFFLHKGTEKNPEISFT
QSSRKQIDNRLPELSHPQSDGVDSTSHTDVKS DPLGHPNSEETVKAKIPSRQOEELPIYSSDFEDVPNKSW
QQTTFQNRPD SRLGKTELSFSSSCEIPHVDGLHSSEELRN LGWDFSQEK PSTTYQQPDSSYGACGGHKYQQ
NAEQYGGTRDYWQNGYWDPRSGRPPGTGVVYDRTQGQVPDSLTDREEEENWDQQDGSFSDQSDKFLLS
LQDKG SVQAPEISSNSIKDTLAVNEKKDFSKNLEKNDIKDRGPLKKRRQEI ESDSES DGELQDRKKVRVE
VEQGETSVPPGSALVGPSCVMDDFRDPQRWKECAKQGMPCYFDLIEENVYLTERKKNKSHRDIKRMQCEC
TPLSKDERAQGEIACGEDCLNRLLMIECSSRCPNGDYCSNRRFQRKQHADVEVILTEKKGWGLRAAKDLPS
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GQLRVGFFTTKLVP SGSELTFDYQFQRYGKEAQKCFGSANCRGYLGGENRV SIRAAAGGKMKKERSRKKDS
VDGELEALMENEGELSDKNQVLSLSRLMVRIETLEQKLTCELIQNTHSQSCLKSFLERHGLSLLWIWMAE
LGDGRESNQKLQEEIIKTLEHLPIPTKNMLEESKVLPIIQRWSQTKTAVPPLSEGDGYSSENTSRAHTPLN
TPDPSTKLSTEADTDTPKKLMFRRLKIISENSMDSAISDATSELEGKDGKEDLDQLENVPVEEEEEELOSQQ
LLPQQLPECKVDSETNIEASKLPTSEPEADAEIELKESNGTKLEEPINEETPSQDEEEGVSDVESERSQEQ
PDKTVDISDLATKL LDSWKDLKEVYRIPKKSQTEKENTTERGRDAVGFRDQTPAPKTPNRSRERDPDKQT
QNKEKRKRSSSLSPSSAYERGTRPD DRYDTPTS KKKVRIKDRNKLSTEERRKLFEQEAQREAAQKQQQQ
MQNLGMTSPLPYDSL GYNAPHHFAGYPPGYPMQAYVDPSNPNAGKVLLPTPSMDPVCSPAPYDHAQPLVG
HSTEPLSAPPPVPVPHVAAPVEVSSSQYVAQSDGVVHQDSSVAVLPVPAPGPVQGNYSVWDSNQSVSV
QQQYSPAQSQATIYYQGQTCPTVYGVTS PYSQTTPIVQSYAQPSLQYIQGQQIFTAHPQGVVVQPAAAVT
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VGRI TTTTEDFKHLARKLTHGVMNKELKYCKNPEDLECNENVKHKTKKEYIKKYMQKFGAVYKPKEDTELE

Confidently predicted domains, repeats, motifs and features:

name	begin	end	E-value
<u>Pfam:AT hook</u>	47	60	1.80E+01
<u>low complexity</u>	230	243	-
<u>low complexity</u>	327	338	-
<u>low complexity</u>	371	400	-
<u>low complexity</u>	505	530	-
<u>coiled coil</u>	549	621	-
<u>AWS</u>	636	682	8.80E-18
<u>SET</u>	683	811	6.00E-41
<u>PostSET</u>	812	828	7.40E-04
<u>low complexity</u>	1080	1093	-
<u>low complexity</u>	1118	1129	-
<u>low complexity</u>	1138	1158	-
<u>low complexity</u>	1271	1287	-
<u>VWV</u>	1361	1393	4.10E-08
<u>low complexity</u>	1447	1468	-
<u>low complexity</u>	1469	1497	-

These features and domains are not shown in the diagram, either because their scores are less significant than the required threshold, or because they overlap with some other source of annotation:

name	begin	end	E-value	reason
<u>low complexity</u>	36	50	-	overlap
<u>low complexity</u>	532	554	-	overlap
<u>low complexity</u>	569	615	-	overlap
<u>Pfam:SET</u>	677	811	8.80E-48	overlap
<u>low complexity</u>	734	739	-	overlap
<u>Pfam:VWV</u>	1362	1391	1.90E-08	overlap

Figure 31 LIN(n3628) Functional domains

Confidently predicted domains, repeats, motifs and features:

name	begin	end	E-value
<u>low complexity</u>	387	411	-
<u>low complexity</u>	435	449	-
<u>AWS</u>	845	900	7.50E-30
<u>SET</u>	901	1024	3.10E-41
<u>PostSET</u>	1025	1041	2.50E-05
<u>low complexity</u>	1262	1286	-
<u>low complexity</u>	1333	1344	-
<u>low complexity</u>	1425	1437	-
<u>coiled coil</u>	1468	1491	-
<u>low complexity</u>	1569	1589	-
<u>low complexity</u>	1605	1619	-
<u>low complexity</u>	1622	1643	-
<u>low complexity</u>	1690	1710	-
<u>WW</u>	1741	1773	2.10E-11

These features and domains are not shown in the diagram, either because their scores are less significant than the required threshold, or because they overlap with some other source of annotation:

name	begin	end	E-value	reason
<u>Pfam:SET</u>	895	1024	6.30E-52	overlap
<u>low complexity</u>	1477	1493	-	overlap
<u>low complexity</u>	1726	1744	-	overlap
<u>Pfam:WW</u>	1742	1771	6.90E-12	overlap

Figure 32 KIAA1732 Domains

SEQUENCE LISTING

<110> MASSACHUSETTS INSTITUTE OF TECHNOLOGY et al.

<120> RB PATHWAY AND CHROMATIN REMODELING
GENES THAT ANTAGONIZE LET-60 RAS SIGNALING

<130> 01997/548WO3

<150> 60/437,821

<151> 2003-01-02

<150> 60/410,160

<151> 2002-09-12

<160> 36

<170> FastSEQ for Windows Version 4.0

<210> 1

<211> 853

<212> PRT

<213> Caenorhabditis elegans

<400> 1

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			20					25					30		
Ser	Asp	Ser	Glu	Pro	Asp	Thr	Ile	Glu	Gln	Leu	Lys	Ala	Glu	Gln	Arg
			35				40					45			
Glu	Val	Met	Ala	Asp	Ala	Ala	Asn	Gly	Ser	Glu	Val	Asn	Gly	Asn	Gln
	50					55					60				
Glu	Asn	Gly	Lys	Glu	Glu	Ala	Ala	Ser	Ala	Asp	Val	Glu	Val	Ile	Glu
65					70					75				80	
Ile	Asp	Asp	Thr	Glu	Glu	Ser	Thr	Asp	Pro	Ser	Pro	Asp	Gly	Ser	Asp
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Trp	Ser	Thr	Ile	Glu	Asn	His	Phe	Thr	Leu	Ser	Ser	His	Glu	Lys	Val
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Val	Glu	Arg	Leu	Ile	Leu	Ser	Phe	Leu	Gln	Val	Phe	Cys	Asn	Thr	Ser
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Pro	Gln	Phe	Ile	Ala	Glu	Asn	Asn	Thr	Gln	Gln	Leu	Arg	Lys	Leu	Met
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Leu	Glu	Ile	Ile	Leu	Arg	Leu	Ser	Asn	Val	Glu	Ala	Met	Lys	His	His
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Ser	Lys	Glu	Ile	Ile	Lys	Gln	Met	Met	Arg	Leu	Ile	Thr	Val	Glu	Asn
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Glu	Glu	Asn	Ala	Asn	Leu	Ala	Ile	Lys	Ile	Val	Thr	Asp	Gln	Gly	Arg
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Ser	Thr	Gly	Lys	Met	Gln	Tyr	Cys	Gly	Glu	Val	Ser	Gln	Ile	Met	Val
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Asp	Met	Phe	Asn	Ile	Lys	Glu	His	Lys	Ala	Pro	Pro	Ser	Thr	Ser	Ser
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Asp	Glu	Gln	Val	Ile	Thr	Glu	Tyr	Leu	Lys	Thr	Cys	Tyr	Tyr	Gln	Gln
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Met	Ile	Pro	Ser	Ala	His	Gln	Ser	Thr	Lys	Val	Leu	Leu	Glu	Val	Pro
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Tyr	Leu	Val	Ile	Phe	Phe	Tyr	Gln	His	Phe	Lys	Thr	Ala	Ile	Gln	Thr
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Glu	Ala	Leu	Asp	Phe	Met	Arg	Leu	Gly	Leu	Asp	Phe	Leu	Asn	Val	Arg
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Lys	Ile	Pro	Ala	Phe	Met	Asp	Leu	Ile	Met	Gln	Asn	Gly	Pro	Leu	Leu
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Val	Ser	Gly	Thr	Met	Gln	Met	Leu	Glu	Arg	Cys	Pro	Ala	Asp	Leu	Ile
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Ser	Val	Arg	Arg	Glu	Val	Leu	Met	Ala	Leu	Lys	Tyr	Phe	Thr	Ser	Gly
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Glu	Met	Lys	Ser	Lys	Phe	Phe	Pro	Met	Leu	Pro	Arg	Leu	Ile	Ala	Glu
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Glu	Val	Leu	Gly	Thr	Gly	Phe	Thr	Ala	Ile	Glu	His	Leu	Arg	Val	
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Phe	Met	Tyr	Gln	Met	Leu	Ala	Asp	Leu	Leu	His	His	Met	Arg	Asn	Ser
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Leu	His	Asp	Pro	Asn	Asn	Ser	Ser	Gln	Val	Gln	Ile	Met	Ser	Ala	Arg		
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Leu	Leu	Asn	Ser	Leu	Ala	Glu	Ser	Leu	Cys	Lys	Met	Asp	Ser	His	Asp		
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Thr	Phe	Gln	Thr	Arg	Asp	Leu	Leu	Ile	Glu	Ile	Leu	Glu	Ser	His	Val		
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Ala	Lys	Leu	Lys	Thr	Leu	Ala	Val	Tyr	His	Met	Pro	Ile	Leu	Phe	Gln		
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Ala	Glu	Lys	Pro	Gly	Met	Asn	Ile	Pro	Lys	Asp	Thr	Ile	Arg	Gly	Val		
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Pro	Lys	Arg	Arg	Ile	Arg	Arg	Leu	Ser	Ile	Asp	Ser	Val	Glu	Glu	Leu		
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Glu	Phe	Leu	Ala	Ser	Glu	Pro	Ser	Thr	Ser	Glu	Asp	Ala	Asp	Glu	Ser		
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Thr	Cys	Lys	Phe	Val	Thr	Gly	Gln	Leu	Arg	Ile	Ala	Arg	Pro	Ser	Gln		
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Asp	Met	Tyr	His	Cys	Ser	Lys	Glu	Arg	Asp	Leu	Phe	Glu	Arg	Leu	Leu		
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Asp	Ile	Leu	Tyr	Gly	Lys	Phe	Leu	Gln	Leu	Leu	Pro	Asn	Leu	Leu	Gln		
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Met	Arg	Glu	Leu	Phe	Val	Glu	Leu	Cys	Leu	Thr	Val	Pro	Val	Arg	Leu		
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Ser	Ser	Leu	Leu	Pro	Tyr	Leu	Pro	Leu	Leu	Met	Asp	Pro	Leu	Val	Cys		
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Ala Met Asn Gly Ser Pro Asn Ile Val Thr Gln Gly Leu Arg Thr Leu	865	870	875	880
Glu Leu Cys Val Asp Asn Leu Gln Pro Glu Tyr Leu Leu Glu Asn Met	885	890	895	
Leu Pro Val Arg Gly Ala Leu Met Gln Gly Leu Trp Arg Val Val Ser	900	905	910	
Lys Ala Pro Asp Thr Ser Ser Met Thr Ala Ala Phe Arg Ile Leu Gly	915	920	925	
Lys Phe Gly Gly Ala Asn Arg Lys Leu Leu Asn Gln Pro Gln Ile Leu	930	935	940	
Gln Val Ala Thr Leu Gly Asp Thr Val Gln Ser Tyr Ile Asn Met Glu	945	950	955	960
Phe Ser Arg Met Gly Leu Asp Gly Asn His Ser Ile His Leu Pro Leu	965	970	975	
Ser Glu Leu Met Arg Val Val Ala Asp Gln Met Arg Tyr Pro Ala Asp	980	985	990	
Met Ile Leu Asn Pro Ser Pro Ala Met Ile Pro Ser Thr His Met Lys	995	1000	1005	
Lys Trp Cys Met Glu Leu Ser Lys Ala Val Leu Leu Ala Gly Leu Gly	1010	1015	1020	
Ser Ser Gly Ser Pro Ile Thr Pro Ser Ala Asn Leu Pro Lys Ile Ile	1025	1030	1035	1040
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Tyr Thr Cys Pro Arg Glu Ser Asp Arg Glu Leu Phe Val Asn Ala Leu	1060	1065	1070	
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Tyr Ser Lys Phe Phe Ile Lys Val Leu Arg Gln Phe Ala Leu Ile Gly	1090	1095	1100	
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Glu Gly Val Leu Pro Leu Cys Leu Asp Ser Ser Val Met Val Asp Ala	1125	1130	1135	
Leu Ile Ile Cys Leu Ser Glu Thr Ser Ser Ser Phe Ile Ile Ala Gly	1140	1145	1150	
Val Met Ser Leu Arg His Ile Asn Glu Thr Leu Ser Leu Thr Leu Pro	1155	1160	1165	
Asp Ile Asp Gln Met Ser Lys Val Pro Met Cys Lys Tyr Leu Met Glu	1170	1175	1180	
Lys Val Phe Lys Leu Cys His Gly Pro Ala Trp Tyr Ala Arg Ser Gly	1185	1190	1195	1200
Gly Ile Asn Ala Ile Gly Tyr Met Ile Glu Ser Phe Pro Arg Lys Phe	1205	1210	1215	
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Leu Gly Thr Val Glu Glu Ile Ser Ser Gly Ser Ala Asp Ser Ala Tyr	1235	1240	1245	
Asp Cys Leu Lys Lys Met Met Arg Val Tyr Phe Ile Lys Glu Glu Gly	1250	1255	1260	
Gln Glu Glu Glu Asn Leu Thr Leu Ala Thr Ile Phe Val Ser Ala Ile	1265	1270	1275	1280
Ser Lys His Tyr Phe His Ser Asn Glu Arg Val Arg Glu Phe Ala Ile	1285	1290	1295	
Gly Leu Met Asp His Cys Met Val His Ser Arg Leu Ala Pro Ser Leu	1300	1305	1310	
Asp Lys Phe Tyr Tyr Arg Phe Lys Glu Phe Phe Glu Pro Glu Leu Met	1315	1320	1325	

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Tyr Lys Val Pro Lys Leu Ile Leu Asn Thr Phe Leu Arg Tyr Leu Arg
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 Ser Met Gln His Val Lys Ala Leu Gln Tyr Leu Val Ile Pro Thr Leu
 1875 1880 1885
 His Trp Ala Phe Glu Arg Tyr Asp Thr Asp Glu Ile Val Gly Thr Ala
 1890 1895 1900
 Pro Ile Asp Asp Ser Asp Ser Ser Met Asp Val Asp Pro Ala Gly Ser
 1905 1910 1915 1920
 Ser Asp Asn Leu Val Ala Arg Leu Thr Ser Val Ile Asp Ser His Arg
 1925 1930 1935
 Asn Tyr Leu Ser Asp Gly Met Val Ile Val Phe Tyr Gln Leu Cys Thr
 1940 1945 1950
 Leu Phe Val Gln Asn Ala Ser Glu His Ile His Asn Asn Asn Cys Lys
 1955 1960 1965
 Lys Gln Gly Gly Arg Leu Arg Ile Leu Met Leu Phe Ala Trp Pro Cys
 1970 1975 1980
 Leu Thr Met Tyr Asn His Gln Asp Pro Thr Met Arg Tyr Thr Gly Phe
 1985 1990 1995 2000
 Phe Phe Leu Ala Asn Ile Ile Glu Arg Phe Thr Ile Asn Arg Lys Ile
 2005 2010 2015
 Val Leu Gln Val Phe His Gln Leu Met Thr Thr Tyr Gln Gln Asp Thr
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10

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Lys

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Pro Ala Tyr Pro Gln Gln Pro Ile Met Leu Thr Met Asp Thr Leu Pro				
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Pro Asn Asp Arg Leu Gly Glu Leu Tyr Glu Lys Ala Ser Ile Glu Gln				

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Leu Ala			
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catgaaaaac tgaataaaaa ttgatatctt taccttatag gctctttaag ggcgcagaca			9163
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gaaaaaaaaa atgtcgggtt ttcgaatttt cgattttcaa agaaaaaaat caatatttaa			9343
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ttttccggaa ttttaataaa aaatcaattt tcgcgtaaca aaaatgcgaa aaaatgacta			9463
gccactcgaa tataataaca catgaaataa aattaaaatt attacag t caa cga gat			9520
		Gln Arg Asp	
		1315	
gca att gtg aga caa gaa ctt gag ctg ata cgt att caa atc gaa aga			9568
Ala Ile Val Arg Gln Glu Leu Glu Leu Ile Arg Ile Gln Ile Glu Arg			
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aaa act gct caa aaa gaa gcg atc aag gcc gct tgc cgt cgt gct aac			9616
Lys Thr Ala Gln Lys Glu Ala Ile Lys Ala Ala Cys Arg Arg Ala Asn			
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Glu Glu Glu Ala Lys Arg Gln Glu Ala Leu Ala Lys Thr Lys Tyr Val			
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Trp Ala Ile Ala Lys Ser Glu Ala Gly Glu Thr Tyr Tyr Tyr Asn Lys			
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Ile Thr Lys Glu Thr Gln Trp Thr Ala Pro Thr Pro Val Gln Gly Leu			
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Leu Glu Pro Ala Cys Gly Ala Ser Pro Asp Thr Thr Val Val Ile Ala			
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Asp Glu Ile Thr Glu Glu Glu Gln Gln Ala Glu Val Leu Glu Lys Pro			
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Arg Val Val Lys Glu Glu Val Ile Glu Pro Gly Ser Gln Ser Glu Thr			
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Gln Lys Glu Ser Pro Glu Lys Val Arg Val Val Val Pro Lys Val Glu			
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 Val Lys Asn Tyr Val Lys Ser Tyr Ile Asp Arg
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Asn	Thr	Pro	Ser	Thr	Ser	Ser	Asn	Leu	Val	Asp	Asp	Lys	Leu	Leu	Ile
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Leu	Glu	Lys	Glu	Val	Glu	Glu	Ile	Glu	Asp	Ser	Ser	Asp	Ile	Leu	Pro
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Asp	Lys	Ile	Asn	Ser	Pro	Glu	Lys	Pro	Ser	Val	Leu	Val	Lys	Arg	Arg
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Ser	Leu	Pro	Leu	Val	Glu	Pro	Ile	Glu	Asp	Ile	Val	Glu	Pro	Asn	Glu
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Pro	Thr	Ser	Ser	Ala	Asp	Pro	Pro	Val	Ser	Asn	Ile	Lys	Asp	Glu	Asp
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Thr	Phe	Lys	Lys	Ala	Ala	Asn	Ile	Pro	Ile	Leu	Lys	Thr	Ser	Ala	Phe
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Ser	Leu	Ser	Glu	Val	Asn	Ser	Ser	Thr	Ser	Ile	Ala	Ser	Glu	Ser	Ser

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Val Ile Arg Asn Lys	Lys His Ala Arg Lys	Val Ile Thr Ile Ala Ser
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Ala Met Thr Asp Tyr	Ser Gln Arg Val Asp	Val Ile Gln Glu Ile Phe
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Ser Ser Asp Thr Ser	Val Thr Val Gln Lys	Phe Tyr Ala Lys Glu Gly
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Met Ala Thr Leu Met	Ala Glu Trp Leu Ser	Glu Asp Asp Tyr Ser Leu
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Asp Asn Leu Lys Leu	Val Gln Ala Ile Leu	Lys Ala Leu His Thr Glu
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Leu Phe Asp Ser Cys	Ala Lys Asn Asp Arg	Leu Leu Arg Asp Ser Thr
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Ser Arg Trp Val Asn	Ala Lys Met Asp Glu	Tyr Val Asp Ile Gln Val
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Ile Ala Asp Ser Leu	Ile Ala Cys Val Glu	Asp Pro Val Gln Glu Tyr
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Lys Asp Val Cys Lys	Val Ile Glu Lys Gly	Leu Val Glu Asn Phe Thr
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Arg Ala Lys Glu Met	Ala Tyr Arg Leu Asn	Gln Tyr Trp Phe Asn Arg
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Ser Val Ser Phe Lys	Ile Pro Lys Lys Ile	Arg Asp Pro Val Pro Lys
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Asp Val Pro Val Arg	Gln Glu Asp Ala Thr	Thr Ser Ser Gln Ser His
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Asp Asn Ser Ser Arg	Thr Val Ser Pro Asn	His Arg His His Ser Ser
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Ser Tyr Ser Asn Ser	Cys Tyr Gln Glu Arg	Glu Pro Ser His Ile Arg
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Phe Phe Asn Asn Gly	Asn Asp Val His Gln	Tyr Arg Phe Gly Gly Tyr
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Arg Asn Tyr Lys Arg	Leu Asp Ile Arg Gly	Ala Arg Ile Lys Thr Ile
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Lys Glu Asp Leu Glu	Ala Ala Ala Ala Ala	Ala Ala Ala Val
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Lys Thr Lys Tyr Val Trp	Ala Ile Ala Lys Ser	Glu Ala Gly Glu Thr
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 Val Leu Lys
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 His Lys Lys His Met Ile Ser Thr
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<213> *Caenorhabditis elegans*

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Ile Leu Asp Asn Gly Lys Ala Glu Glu Gly Thr Asp Glu Asp Ser Asp
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Leu Val Glu Gly Ile Leu Asn Ala Asn Ser Asp Val Gln Ala Leu Leu
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Asp Ala Pro Ser Glu Gln Val Ala Gln Ala Leu Asn Ser Phe Phe Gly
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Asn Glu Ser Glu Gln Glu Ala Val Ala Ala Gln Arg Arg Val Asp Ala
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Glu Lys Thr Ala Lys Asp Glu Ala Glu Leu Lys Gln Gln Glu Glu Ala
115          120          125
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- 80 -

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- 86 -

-87-

-87-

- 88 -

- 89 -

1905

1910

1915

